MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

HYATT REGENCY

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IRVINE, CALIFORNIA

TUESDAY, DECEMBER 4, 2007

9:04 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Katharine Hammond

Dr. Joseph Landolph

Dr. Charles Plopper

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Aguila, Manager, Substance Evaluation Section

Mr. Lyn Baker, Air Pollution Specialist

Mr. Jim Behrmann, Liaison, SRP

Ms. Janette Brooks, Chief, Air Quality Measures Branch

Ms. Susie Chung, Air Pollution Specialist

Mr. Peter Mathews

Dr. Brent K. Takemoto, Air Pollution Specialist

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

Dr. Tobi L. Jones, Assistant Director

Dr. Joseph Frank, Senior Toxicologist

Dr. Marilyn H. Silva, Staff Toxicologist, Specialist

APPEARANCES CONTINUED

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Dr. George Alexeeff, Deputy Director

Dr. Melanie Marty, Manager, Air Toxicology and Epidemiology Section

Dr. Andrew Salmon, Chief, Air Toxicology and Risk Assessment Section

Dr. Charles Vidair, Pesticide and Food Toxicology Section

Dr. Bruce Winder, Toxicology & Risk Assessment Section

ALSO PRESENT

Dr. Ed Matthews, U.S. Food and Drug Administration

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PROCEEDINGS

CHAIRPERSON FROINES: Let's begin. Let's call the December 4th, 2007, meeting to order.

And the first topic on the agenda is the continuation of the Panel's review of the endosulfan report.

So, Tobi, you're on.

DPR ASSISTANT DIRECTOR JONES: I just want to make a couple of comments.

We provided the Panel copies of the revised risk assessment. I want to apologize that the Executive Summary paper copy that we provided to you does not include all of the changes in the text itself. And Peter is providing you a copy of that now. And I apologize for that. I think if you'd gone into the electronic versions, it represented more changes.

But I will point out that because we weren't able to get feedback on elements of the exposure assessment by the time we provided the copy, that we will need to make some changes in the Executive Summary relative to the exposure assessment.

Marilyn Silva is here and, as needed, can discuss with you changes in the risk assessment itself. Joe Frank is here representing Cheryl Beauvais, who was unable to travel to the meeting today, to address changes or answer

any of your questions regarding the exposure assessment.

CHAIRPERSON FROINES: So if I understand what you're saying, is that you're anticipating comments on exposure assessment today from the Panel and that you'll then use any of those comments, plus what you've already done, to improve the Executive Summary?

DPR ASSISTANT DIRECTOR JONES: There are -- I believe there are changes in the exposure assessment that were made, and Joe can discuss those. We have not -- we are interested in feedback from the Panel.

CHAIRPERSON FROINES: Great. That's fine.

Is that fine?

PANEL MEMBER FRIEDMAN: Can I ask a question?

CHAIRPERSON FROINES: Sure.

PANEL MEMBER FRIEDMAN: Who was the audience for the Executive Summary?

DPR ASSISTANT DIRECTOR JONES: The audience for the Executive Summary is the Panel. And it is part of our rationale for proposing endosulfan as a toxic air contaminant.

PANEL MEMBER FRIEDMAN: Because there are things in here I -- vocabulary that I did not understand. And I'm not sure if that's a problem or not. For example, I didn't understand what chemigation was, rights-of-way sprayer, dip treatment, things like that. And I'm not

sure if this is directed just toward people who use pesticides. I'm sure they understand it fully. But I don't -- I have no idea what that means. So --

DPR ASSISTANT DIRECTOR JONES: I understand.

PANEL MEMBER FRIEDMAN: So I mean if you -- I'm not sure if this calls for a change in the Executive Summary so you can explain it a little more. But I'd appreciate it if that were the case.

DPR ASSISTANT DIRECTOR JONES: Okay.

CHAIRPERSON FROINES: That's good.

Yeah, an executive summary presumably will be read by people who wouldn't read the entire document. So it should be the most clearly written of all the sections, in a sense. Not to say other sections shouldn't be clearly written.

But the other thing is the Executive Summary can serve a useful purpose for us in developing our findings. So I think that our findings -- we'd want to have things clear so that if we wanted to incorporate any of that from the Executive Summary, that would be -- we don't want things we don't understand.

You're face is blank.

PANEL MEMBER FRIEDMAN: What's the point you're trying to make? I'm sorry.

CHAIRPERSON FROINES: Oh. I'm just saying

that -- I'm just agreeing with you, and that -- because I think we may use parts of the Executive Summary for writing the findings. And if there are comments in there that we don't understand, then that shouldn't be the case.

PANEL MEMBER FRIEDMAN: Well, since you mentioned our findings, I would also like to raise the question of, should our findings be so detailed? It's got tables and a lot of text with detailed information. Can we just come to some conclusion that, you know, for these various reasons this is a toxic air contaminant; you know, it affects this and that and the level is below the margin of error? You know, as someone said at breakfast, maybe it should just be one page. And, you know, it's so detailed. And I'm just wondering if that's appropriate for our --

CHAIRPERSON FROINES: No, I wasn't saying that we were going to use the whole document or the OEHHA findings in their total. All I was saying is if we take anything out of it, we just want to make sure it's clear.

You're now raising a second question.

PANEL MEMBER FRIEDMAN: -- question, right.

CHAIRPERSON FROINES: And given our dinner last night, I can say that you have been historically the person who most -- have been most articulate about short findings.

And so why don't we have a discussion about that

today for the whole panel, who may not have been at breakfast this morning. And I don't think anybody -- I actually think you won't find any disagreement with short findings. But let's wait -- let's let DPR go ahead and --

PANEL MEMBER FRIEDMAN: Just to say, they used to be short and now they're getting longer and longer.

CHAIRPERSON FROINES: Well, since this is our hundredth meeting --

(Laughter.)

CHAIRPERSON FROINES: -- I can honestly say that there's a certain sinusoidal quality to them. They go up and down over the years. And usually it -- when it's down, it's because you've said something. The history of the length of the findings and Gary Friedman's comments on this is -- there's a certain correlation that we could make that would statistically significant.

Go ahead, Tobi.

DPR ASSISTANT DIRECTOR JONES: Well, I think I'd like to turn it over to staff.

CHAIRPERSON FROINES: Great.

DPR ASSISTANT DIRECTOR JONES: Would you like the exposure assessment discussed -- changes in the exposure assessment discussed first?

CHAIRPERSON FROINES: Sure. Sure, you're call.

DPR ASSISTANT DIRECTOR JONES: Joe Frank will be

discussing that.

DPR SENIOR TOXICOLOGIST FRANK: Excuse me just a moment. I'm loading the jump drive.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: I think this is one that's being used right now.

CHAIRPERSON FROINES: While we're waiting, I should tell you that we have to end today at 3:30. We can't go longer. I have a class at 6 o'clock. And Barbara Pitts yesterday said I'll never make it if we try and leave at 4. It's on the risk assessment of nanotechnology.

PANEL MEMBER BLANC: That should be a very short lecture.

(Laughter.)

CHAIRPERSON FROINES: I'm trying to show them the broad picture.

PANEL MEMBER BLANC: To paraphrase Churchill, "Never has so much been said about so little."

(Laughter.)

DPR SENIOR TOXICOLOGIST FRANK: Okay, Dr. Froines. I'm ready.

CHAIRPERSON FROINES: Thank you.

(Thereupon an overhead presentation was Presented as follows.)

DPR SENIOR TOXICOLOGIST FRANK: My name is Joseph Frank. I'm the Senior Toxicologist. I manage the Exposure Assessment Program at Department of Pesticide Regulation. And Dr. Cheryl Beauvais does work in my group.

Cheryl, as you know, had some health issues and was unable to travel, so she sent me as a substitute.

Basically we had three areas that seemed to be of significant concern to the Panel that we did address in the exposure assessment document itself. And as Tobi indicated, the exposure assessment has been modified to make those changes -- to include those changes, and we would like your feedback.

The Executive Summary and the risk characterization has not been modified as of yet. And we will do that after we hear comments from the Panel.

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DPR SENIOR TOXICOLOGIST FRANK: The three areas that were of concern, our appreciation anyway of it, was that endosulfan-related illnesses -- there are a number of illnesses that were not clear to the Panel and so we made an extra effort to go through and describe the illnesses and exactly what each represented.

The next one was more of a significant issue, in our opinion. And that was, there was a significant

concern by several Panel members of the study that we're using for ambient air monitoring. We do think that we addressed that in a sufficient way to satisfy the Panel, and we would like your feedback. And I'll get to that in just a moment.

And then the final issue was particulate matter that Dr. Hammond brought up. And so we added additional documentation and comments to the exposure assessment to make sure that we're acknowledging that potential issue.

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DPR SENIOR TOXICOLOGIST FRANK: Reported illnesses is pretty much we went through and made sure that we explained in more detail what case was, where case is an individual episode where we have a number of individuals involved. We also discussed such issues as systemic illnesses, which as indicated on this slide include such things as nausea, dizziness, and headaches and numbness.

And endosulfan --

CHAIRPERSON FROINES: Would you go back to that.

DPR SENIOR TOXICOLOGIST FRANK: Certainly.

Yeah. So a case is a person whose health problems may relate to pesticide exposure. An episode is an event in which a single source appears to have been the problem. And there may be one or more people or cases.

CHAIRPERSON FROINES: What do you mean by "source"?

DPR SENIOR TOXICOLOGIST FRANK: An event is essentially when we have a reported incident.

CHAIRPERSON FROINES: Okay.

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DPR SENIOR TOXICOLOGIST FRANK: For endosulfan, only cases -- there were seven.

Two were basically people complained primarily of irritation. And as indicated, there is a greenhouse applicator and a grape harvester.

Two complained of systemic symptoms.

And then there was three additional that complained of both irritation and systemic.

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DPR SENIOR TOXICOLOGIST FRANK: And this is all documented in the exposure assessment in the latest version.

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DPR SENIOR TOXICOLOGIST FRANK: All cases, there's -- Cheryl put together a summary table. So we have endosulfan alone. And we've broken it down so we can see which ones are endosulfan only, endosulfan with other pesticides, and then total in which endosulfan was involved.

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DPR SENIOR TOXICOLOGIST FRANK: The issue that --

PANEL MEMBER HAMMOND: Excuse me. Would you prefer if I interrupt you as we go along --

DPR SENIOR TOXICOLOGIST FRANK: Not at all. Please --

PANEL MEMBER HAMMOND: -- or hold it till the end? Which would you prefer?

DPR SENIOR TOXICOLOGIST FRANK: As I go would be fine.

PANEL MEMBER HAMMOND: Okay. Since you have three main areas and you're finishing illnesses, may I ask some questions about illnesses then?

DPR SENIOR TOXICOLOGIST FRANK: Certainly, absolutely.

PANEL MEMBER HAMMOND: Okay, great. Thank you.

So, first -- this is kind of a -- between your document and OEHHA's findings there's a discrepancy in the numbers. OEHHA says there were 63 cases and you say 58. So just somehow that should get reconciled.

DPR SENIOR TOXICOLOGIST FRANK: Oh, certainly. We'll --

PANEL MEMBER HAMMOND: And, you know, from the same reporting system. And it's slightly different years, but it still doesn't work out. It looks like 63 from one

fewer year. So I don't understand.

Okay. Then within -- OEHHA also pointed out it was unclear how many of the reported incidents were nonagricultural workers -- were non-occupational I guess was the term used. There was one, as you said, in the seven episodes which were endosulfan only. One of these was a resident, was non-occupational. And for the others, there's a discussion of the 30 cases that were reentry before the reentry interval had passed. But then there's actually not much discussion beyond that. And I think that that -- it would be useful to know more about those other cases.

DPR SENIOR TOXICOLOGIST FRANK: Certainly. Be happy to.

PANEL MEMBER HAMMOND: And particularly since OEHHA brought up this issue of, you know, how many might have been bystanders, that that I think is a good question since there's one of the seven. And I understand there still is that lack of information.

DPR SENIOR TOXICOLOGIST FRANK: Sure. Be happy to.

PANEL MEMBER LANDOLPH: Quick one while we're here.

On a previous slide you had mentioned shortness of breath. Is any of that permanent? Is there any

reactive airways dysfunction syndrome or any permanent lung sequela that result from this exposure?

DPR SENIOR TOXICOLOGIST FRANK: To our knowledge it was not. But often that kind of information is not recorded. And so in many cases we wouldn't know.

PANEL MEMBER LANDOLPH: Thank you.

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DPR SENIOR TOXICOLOGIST FRANK: The issue with ambient air, as we're discussing the concerns of the panel, one of the questions that came up was whether or not we understood where the actual release was and how it related to the monitoring itself: How close was it to the monitoring site? And going through this, we realized that by default the highest exposure for ambient air is going to be bystander. Just as it is with acute, it would be for seasonal as well.

So since Cheryl had calculated a three-day exposure, which is basically greater than acute, if we used that air concentration and we used the study for bystander, by definition we are getting the highest ambient air exposure, because we have people -- I mean we have monitoring adjacent to a field at the time of application. And so by definition, if you have a home or you have individuals, children, adults, whatever, playing adjacent to a field that has been treated, they would by

default get the highest exposure.

So what we've done is we've modified the exposure assessment to use bystander for seasonal as well as acute. And the study we used was a valid study. We did not have problems with the controls. As you may remember the problem with the study that we did have for ambient air, there were a number of control issues.

So I think if you'll look in the revised version of the exposure assessment, I think you'll be satisfied that we do have the worst-case scenario for ambient air and we have a study that is acceptable.

Yes.

PANEL MEMBER HAMMOND: First of all, I meant to say earlier, I would like to apologize to the staff that I didn't get my comments to you before this meeting. Just personal things have just made it too difficult to get that done earlier. So my apologies.

PANEL MEMBER FRIEDMAN: Can you speak into the microphone.

PANEL MEMBER HAMMOND: Oh, I thought I was. Sorry.

My apologies to the staff. You've done all this hard work and I did not get my comments to you sooner before the meeting, and I truly apologize for that.

Okay. So a couple of questions about -- the

ambient was based on August sampling in Fresno County. And clearly June, July, and August were the highest use months in Fresno. As it turned out -- and I think this was not predictable when the sampling was done, so it's not a criticism about the sampling -- turned out that August was the lowest of those three months and was approximately half of what it was in June.

So at the very least I think that there should be a correction made for that, you know, that that's -- approximately a factor of 2 could have been higher in the months when twice as much was used, if you're doing ambient. At least there should be an acknowledgement of that, that when you say it's the highest worst case, I think we have to recognize that it probably misses a little bit by that.

Then in terms of the bystander, I agree with what you've done with that approach, you know, so it makes the other part not so relevant just to say it. But using the bystander does give you a worst-case situation.

On page 81 of the revised document, on the second paragraph on the bystanders, there's a paragraph that describes some of the issues around that. It says, "Concentrations of endosulfan in air might be anticipated to vary with different application methods and with different types of crops." This makes sense. "Factors

affecting drift from spray applications include type of crop, wind velocity and direction, volume and direction of sprayer air jets and nozzles, and application rate. Aerial and air blast applications typically result in a greater spray drift than low pressure boom applications, assuming similar spray droplet size and wind velocity. To decrease the likelihood of underestimating exposures, application site results were corrected for field spike recoveries."

Oh, no that's -- but the real point here was that there were these factors which were identified that would affect bystander. But then I wondered how were those factors -- there's one major bystander study that is relied upon in this. And I wasn't sure whether these factors were at the maximum in that study. In any event, there should be some discussion of how that one study relates to the factors that have been identified as affecting --

DPR SENIOR TOXICOLOGIST FRANK: Sure. Well, if you're asking the question, then there needs to be additional clarity that we'll add to it. But our intent is to -- we either use air blast or aerial applications for bystander because of those issues that you were covering there.

PANEL MEMBER HAMMOND: And then type of crop

was -- it was an orchard. It was an apple orchard.

DPR SENIOR TOXICOLOGIST FRANK: Typically the orchards tend to --

PANEL MEMBER HAMMOND: The highest. So I think it's worth a discussion of saying, "Here are the factors. And where does the one set of sampling fall within those factors?"

DPR SENIOR TOXICOLOGIST FRANK: Yes. And as far as we know, there's -- we do not have any discernable difference between air and ground application when it's done by air blast. So we're essentially assuming that both of those give us the highest value. However, in this case I believe we're using air blast.

PANEL MEMBER HAMMOND: What do you mean there's no different between air -- you mean the air concentration is not different whether it's applied by air or --

DPR SENIOR TOXICOLOGIST FRANK: We're seeing the same sort of high concentrations --

PANEL MEMBER HAMMOND: In the air?

DPR SENIOR TOXICOLOGIST FRANK: -- for bystander exposure after air application or after air blast. Remember, some of these air blasts are getting orchards that trees may be 30 feet high.

PANEL MEMBER HAMMOND: That would be nice to include that information.

DPR SENIOR TOXICOLOGIST FRANK: Certainly. Be happy to.

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DPR SENIOR TOXICOLOGIST FRANK: So, again, after you've had an opportunity to look through that, we'd love to hear any additional comments you may have. But I think we've addressed the concerns. And we agree with the concern that the Panel -- and that's essentially why we made the changes as well.

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DPR SENIOR TOXICOLOGIST FRANK: And this just finishes off by showing that the numbers that were initially used in our calculations -- and when we switched over to bystander for seasonal, you can see that the numbers -- the numbers are higher than the highest value we predicted by the ambient. And we would expect that.

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DPR SENIOR TOXICOLOGIST FRANK: The third section was the particulates. And Dr. Hammond brought this up as well.

This is a tough area. We acknowledge that particulates can play a role. But to the best of our knowledge, it's not a significant role with the pesticides that I've looked at. In this particular case we're not even aware of how we could quantitate it. So we've added

some discussion. We've added some references to the document where we've essentially acknowledged this potential and basically acknowledged that there is potential that we may have missed some exposure because of particulates getting through.

In talking with our resources at the Air Resources Board and Lyn Baker and others, we're fairly confident that it's not a significant loss. But we still should acknowledge that there is potential for an underestimate.

CHAIRPERSON FROINES: Well, I have a question about that. Lyn or Kathy may want to comment.

Endosulfan has a low vapor pressure. It's not exactly telone, for example. And so given its molecular weight and low vapor pressure, I would anticipate that a fair amount would be absorbed on particles -- adsorbed to particles. And so I'm not sure that it's a trivial issue actually. I'm not sure I agree with you that it's a trivial issue.

You can look at that question about what you would think would be the adsorption characteristics. But I'm not so sure. I mean given the high molecular weight, it's going to go straight to particles.

PANEL MEMBER ATKINSON: Well, it does appear to be distributed between gas and particle phase.

CHAIRPERSON FROINES: Pardon me?

PANEL MEMBER ATKINSON: It is apparently distributed between gas and particle phase.

CHAIRPERSON FROINES: Yeah, I would expect so.

PANEL MEMBER ATKINSON: So it will depend upon temperature and it will also depend upon particle loading.

CHAIRPERSON FROINES: Yeah. And --

PANEL MEMBER HAMMOND: And it's apparent -- even in the references that you cite, you point out that in some cases all of the endosulfan was collected in gas phase and then you say while others in other studies are particle-bound endosulfan -- this is on page 80, in the highlighted section -- and in these other studies, particle-bound endosulfan either equal or exceeded the amounts received in gas phase.

And, by the way, one of those references was missing -- you need to add the shower reference was missing.

DPR SENIOR TOXICOLOGIST FRANK: Thank you.

PANEL MEMBER HAMMOND: So there is evidence actually ambiently that the particle phase can exceed. And, yes, exactly, it's going to vary by a set of environmental conditions.

CHAIRPERSON FROINES: Well, as I look at the structure of endosulfan, it looks to me like, yes, you'll

see vapors, gas phase because of the nature of the spraying. But to the degree that you have a high particulate load in any area, this stuff is going to -- this is going to adsorb to particles very rapidly. Its vapor pressure is non -- you know.

PANEL MEMBER ATKINSON: I mean it's like a PCB in essence. It's got a vapor pressure not much different than some of the PCBs. And it looks like -- at least from its worldwide distribution, it looks like it behaves to a certain extent quite analogous to PCBs.

PANEL MEMBER HAMMOND: Off and on, off and on.

PANEL MEMBER ATKINSON: Well, the other thing -- I mean particles are trapped so that -- I haven't read all this lot. I have to acknowledge that.

So we found that particles will under some conditions go through polyurethane foam plugs quite surprisingly. We were surprised at that. So I think you've got to be very careful about the fact that particles are going to be trapped by a bed of resin.

PANEL MEMBER HAMMOND: And, again, I would remind you that I beside -- I think it was Joan Daisey's work on styrene which definitely showed that particles -- spray particles of styrene passed through the absorbent tubes, which was a surprise again. I mean I was surprised when I first saw that. It is counterintuitive. But it turns out

that experiment after experiment where they really looked at it has found a significant amount of particle penetration in absorbent tubes. So assuming it's not sufficient.

DPR SENIOR TOXICOLOGIST FRANK: From our understanding, it can even be more complicated. As the particles are passing through, they're exchanging endosulfan. I mean it's quantitated. I'm not sure how to deal with that.

PANEL MEMBER HAMMOND: Oh, you know, in fact, the reality is those kinds of experiments have been laid out. If you go to the literature, you can find out how to determine that. You can do that. That's not impossible.

DPR SENIOR TOXICOLOGIST FRANK: I believe the Air Resources Board has been tussling with this question as well. And if you permit, perhaps Lyn could help on this issue.

ARB AIR POLLUTION SPECIALIST BAKER: Good morning, members

CHAIRPERSON FROINES: I just want to say that we're particularly interested in this. You know, we have a particle center. But what we've discovered is the enormous amount of molecules that people thought might be particle association are actually in the vapor phase. So this is the reverse of that. And if I was -- well, I'll

agree with Roger that this looks like a PCB in terms of what you would expect in that regard.

ARB AIR POLLUTION SPECIALIST BAKER: Good morning, members of the Panel. Lyn Baker with the Air Resources Board.

And as Joe mentioned, Joe and Cheryl of DPR staff have discussed this with me. And I've actually discussed it with our chief chemist, Mike Poore.

CHAIRPERSON FROINES: Is you're Mike on?

ARB AIR POLLUTION SPECIALIST BAKER: Yeah.

CHAIRPERSON FROINES: Bring it a little closer.

ARB AIR POLLUTION SPECIALIST BAKER: I've discussed it with our chief chemist, Mike Poore. And we certainly recollect this study as well as a study which Joe mentions there in the second bullet, the azinphos-methyl study, which is also a compound of relatively low molecular -- or vapor pressure, I believe. Where many years ago we actually did a comparison with and without a pre-filter prior to the exit -- the resin. And we really didn't see a whole lot of difference in the concentrations. And based on that and based on the fact that DPR was -- whether it was in the particular phase or in the gaseous phase, they were adding it all together for their exposure assessment.

Our lab made the decision at that point that we

didn't need to use pre-filters. We certainly agreed that there can be ultrafine particles that could pass through the XAD bids. Out in the rural areas where we do these studies, I would assume that most of the particulate would be of a larger size and not all the ultrafines maybe that you find in an urban area.

PANEL MEMBER HAMMOND: Well, actually a couple things. Kind of back-up.

I thought I remembered from the September meeting that the pre-filter was not analyzed for the pesticide. Is that not -- maybe I'm remembering wrong. I thought that they were saying there was no difference but the pre-filter had not been analyzed.

ARB AIR POLLUTION SPECIALIST BAKER: Oh, no. In the azinphos-methyl study we had analyzed them both.

PANEL MEMBER HAMMOND: And you analyzed -- but you weren't -- the endosulfan was not part of that?

ARB AIR POLLUTION SPECIALIST BAKER: No, no, no, no.

PANEL MEMBER HAMMOND: You were just using that as an model compound?

ARB AIR POLLUTION SPECIALIST BAKER: That's just as an -- yes, exactly.

PANEL MEMBER HAMMOND: Okay. Yeah, that's exactly what she would want to do.

ARB AIR POLLUTION SPECIALIST BAKER: But as Joe mentioned, we --

PANEL MEMBER HAMMOND: But I also think that there are a lot of fine particles also in agriculture because you get atmospheric chemistry making particles.

ARB AIR POLLUTION SPECIALIST BAKER: That's fine. But I'm not sure about the ultrafines that you would expect associated with combustion in an urban area. I know from experience that, as Jim mentioned, in the first bullet there, we have seen the top of the resin beds that get colored with the particulate. So it does indicate that some of it is being trapped by the resin bed.

Also, our chief chemist pointed out to me that these XAD tubes when they're packed, that they commercially made XAD tubes, have glass wool on top of the XAD resin to hold it in place. So when the top of the glass tube is broken off prior to sampling, the air comes through the opening in the tube and counters that bed of glass wool before it impacts the XAD. He would expect that the glass wool would also act as somewhat of a filter for some particles.

PANEL MEMBER HAMMOND: Again, the studies that Joan Daisey did included those same kind of tubes with the glass wool.

ARB AIR POLLUTION SPECIALIST BAKER: Okay. Well

we may need the relook at those. We may need to --

PANEL MEMBER HAMMOND: And this may be more of, you know, something to just be watching in the future to at least make these assessments.

ARB AIR POLLUTION SPECIALIST BAKER: Yeah.

CHAIRPERSON FROINES: Well, see, the other thing is that, you know, life is changed dramatically as the San Joaquin Valley has many more mobile sources and pollution. And so you have fossil fuel, incomplete combustion, and also you're getting things blown into the valley from San Francisco and the -- my view is that endosulfan's going to have a very strong van der Waals forces holding that will -- if the endosulfan binds with it. And I would suspect that it will be -- it would be an interesting problem of extraction. And so one may need to make sure that the extraction, you know, may use methylene chloride but something also like acetonitrile, and so that you're really trying to get everything off.

Because I think this compound's going to be held very tightly to particles. So that I think this is something that needs a relook. If you have high molecular weight compounds that have a lot of polar groups on them, they're going to stick, I think. And am I -- do you think that's correct? I mean Terrence Brisby's studies --

PANEL MEMBER ATKINSON: I mean they certainly

will -- it all depends upon their red pressure and their essentially optimal water and -- optimal lab partition and water pressure.

CHAIRPERSON FROINES: I was just going to say one other thing.

PANEL MEMBER BLANC: How come we don't have inspirational speakers.

(Laughter.)

PANEL MEMBER BYUS: Cheer. We should have cheering occasionally.

CHAIRPERSON FROINES: I think this is an issue that ARB and DPR should relook at, because I think that we may be missing some exposures, and that wouldn't be done.

Is that a fair conclusion from your standpoint?

ARB AIR POLLUTION SPECIALIST BAKER: That's a good recommendation, Dr. Froines. And as you mentioned, you're correct, that the San Joaquin Valley has a lot more automobiles and combustions and then products of incomplete combustion than it did 20 years ago.

CHAIRPERSON FROINES: Yeah. Well, what I'm saying of course is that you have a lot more particles in the air.

ARB AIR POLLUTION SPECIALIST BAKER: Much more, much more.

CHAIRPERSON FROINES: And so you have more

opportunity for adsorption.

And there was one other thing I was going to say. It'll probably come back to me.

Oh, the other question is: Are you generating many ultrafines that could contain some more volatile compounds by atmospheric chemistry? And I don't know the answer to that.

So I mean -- ultrafines aren't just a product -- aren't just a product of --

PANEL MEMBER HAMMOND: No, that's what I was trying to say. Yes, there definitely are in the Central Valley from agriculture, yeah.

CHAIRPERSON FROINES: So thank you.

DPR SENIOR TOXICOLOGIST FRANK: Sure.

I agree also. You have brought this to our attention and we're definitely discussing it with the Air Resources Board to try and -- we constantly are having new monitoring taking place. We want to make sure that if we can deal with this, we can do it appropriately.

CHAIRPERSON FROINES: Well, let's use a Tisch sampler. And then you can have an XAD. I mean that's what we would use if we were going to do this.

ARB AIR POLLUTION SPECIALIST BAKER: Our lab wouldn't have the resources to put five or six of these --

CHAIRPERSON FROINES: We could loan you them.

No, I'm serious. We have them. You could borrow them.

ARB AIR POLLUTION SPECIALIST BAKER: Well, we can discuss -- we and DPR will definitely talk about this.

CHAIRPERSON FROINES: Then we'll write a paper so we can get something good out of it.

Go ahead. I'm sorry. I'm being -- not using time well.

DPR SENIOR TOXICOLOGIST FRANK: And thank you for your offer.

--o0o--

DPR SENIOR TOXICOLOGIST FRANK: So, in essence, what Cheryl has put together is the rest of that discussion. Fractions of endosulfan and the particulate versus a gas phase varies. Vapor pressure, total suspended particulate concentration and temperature are all factors that are going to impact this. And it's unclear whether an estimate -- an underestimate has occurred. And we believe that it is possible and we do believe that we need to acknowledge it. But to quantitate it, we're not aware of how we could do that.

--o0o--

CHAIRPERSON FROINES: I think it's worth just saying that there is a potential for some underestimation.

DPR SENIOR TOXICOLOGIST FRANK: We agree.

CHAIRPERSON FROINES: You do?

DPR SENIOR TOXICOLOGIST FRANK: Yes. And I believe Air Resources agrees as well.

Any additional questions on the exposure side?

PANEL MEMBER HAMMOND: I just have a few small things.

DPR SENIOR TOXICOLOGIST FRANK: Certainly.

PANEL MEMBER HAMMOND: Let's see. Golf courses were mentioned. One of the incidents was at a golf course. Is endosulfan still being used in golf courses, to your knowledge? One way or the other, I just think that information should be included.

DPR SENIOR TOXICOLOGIST FRANK: Okay.

PANEL MEMBER HAMMOND: Because golf courses can often be nearby residential areas.

DPR SENIOR TOXICOLOGIST FRANK: Yes.

PANEL MEMBER HAMMOND: And so that would be relevant. And similarly greenhouses, the same issue there.

There's a paragraph that's repeated on page 34 and 37. And it really can't be belonging in both places. I think the second is the wrong.

DPR SENIOR TOXICOLOGIST FRANK: Okay. Thank you.

PANEL MEMBER HAMMOND: On page 34 and 37, I think you'll see it.

There's a lack of clarity in the sampling that was done around the application. There's discussion at one point that there were two sampling stations on the north. And in another place in the document it says there were two sampling stations on the south. It gets very confusing.

So, again, if you could just clarify that.

DPR SENIOR TOXICOLOGIST FRANK: Certainly.

PANEL MEMBER HAMMOND: So I think that -- but those are relatively minor. I also think that discussion of the particles that you have on page 80, I would suggest you move that to the section you have on the QC and you have that other discussion about the problems with the field and trip blanks and the recoveries and some of those things. I just would do -- it just seems to me that kind of a QC discussion belongs together. It kind of comes in the middle on page 80 where you're kind of synthesizing a lot of other things. I mean it's just a suggestion. It's not serious.

So just my major points is I do think a little more -- I'm really glad you added the illness. I think that that's useful. But a little more -- to explain a little more on that. To at least mention that the ambient sampling, even though I know later you don't rely on it. But the ambient sampling is not the maximum,

because it was done at a month. It was at half of the maximum usage in the --

DPR SENIOR TOXICOLOGIST FRANK: Right. And since we do present the study, I have no problem presenting that information as well.

PANEL MEMBER HAMMOND: Yeah, you'd just kind of acknowledge that at the end of it, that that's all it takes. I mean, you know, it's what happens when you do this sampling.

And then now I'm going to step out -- totally outside of my area of expertise -- well, there's a discussion in the fate chapter about how in laboratory experiments in the first 24 hours material that's applied to the soil and also to leaves actually evaporates, is back in the air, over half of it within the first 24 hours. Which I should say, I was surprised. I had not realized it was that volatile. It occurred to me one could at least talk about how much is applied in general and just make, you know, like if that were to all evaporate in a time, just some sense of that. Because I know that sometimes when the TAC was being done on diesel, there was a discussion of how much is being emitted into the state. You could talk about that way, just a little bit of that.

Oh, and one final comment. There's a discussion

about how because there's a decrease in the usage of endosulfan, that means there's a decrease in exposures. And I think we have to be careful about that. It may be that there are fewer people exposed. But if they're spraying an orchard, unless they're actually using less on that orchard, the bystander will still have the same exposure. We don't -- and if the uses go down to one-third, it doesn't mean the bystander gets one-third. It just means one-third as many people maybe or something. But we have to be careful about that. And there's a little bit of that in there.

DPR SENIOR TOXICOLOGIST FRANK: We can rephrase that, because I totally agree with you.

PANEL MEMBER ATKINSON: Well, I had some comments on the environmental section. In fact, I typed them up so I can give you them afterwards. But there's certain areas on page 31 -- or 30 that need to be clarified. That's mainly the lab studies that's in there.

Anyway, I've got a write-up and some suggested language. I can give you it.

CHAIRPERSON FROINES: Just from the standpoint of the rest of the Panel members, are there any points that you could bring up now that might be of interest for the rest of the Panel?

PANEL MEMBER ATKINSON: I'm sorry, for --

CHAIRPERSON FROINES: What I'm saying is you're going to give them your written comments. But then nobody else will know what you've given them.

PANEL MEMBER ATKINSON: Oh, that's true, yes.

CHAIRPERSON FROINES: So if there's anything of consequence which you think is worth --

PANEL MEMBER ATKINSON: Well, there's a few strange typos. Also, Riverside County apparently is in the San Joaquin Valley, which I'm surprised at.

DPR SENIOR TOXICOLOGIST FRANK: We moved it.

(Laughter.)

PANEL MEMBER ATKINSON: Oh, okay. Yes.

So it's the stuff that's on page 30, the first full paragraph dealing with the alleged radical reactions in the gas phase. And all those studies are on -- well, at least they're not available in the then sort of normal peer-reviewed literature. So I think some additional details need to be given.

On one of them the stuff by Kloepffer, et al., it's done in solution in actual fact, and it assumes that the solution phase reactivities on a relative basis are equal to the gas phase one. So they measure things relative to toluene in the solution phase and in an inert solvent, and assume that the gas phase reactions have the same relative reactivity. So that needs to be brought

out. And I got an additional reference there for you.

DPR SENIOR TOXICOLOGIST FRANK: Thank you.

PANEL MEMBER ATKINSON: So essentially just tidying that lot up and then tidying up what the overall lifetime would be. Because you're using a rather strange average electronical concentration and lower than what people normally use. And I've got a reference for that.

DPR SENIOR TOXICOLOGIST FRANK: Okay. Thank you.

PANEL MEMBER ATKINSON: And then that needs to be brought over on this -- some of that needs to be tidied up in the Volume 3 -- no, Volume 1 on page 31 and 32. Some of that just needs to be tidied up.

All were fairly minor, but it will make it a lot easier to read.

DPR SENIOR TOXICOLOGIST FRANK: No, we appreciate your comments.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: I had something -- there was something in the Executive Summary on Roman numeral page 8 that puzzled me, and I couldn't immediately find it in the full report. It's about dietary MOEs. And it said something to the effect that tolerance levels of endosulfan for apple, melon, tomato in selected population groups were all, except for seniors 55 years and over, less than a hundred.

Why would there be a difference for -- why would seniors have a different situation with that?

DPR SENIOR TOXICOLOGIST FRANK: Do you want -- that was actually done by medical toxicology. So I'm going to have Marilyn address that when she comes up, if that's all right.

PANEL MEMBER FRIEDMAN: Sure.

PANEL MEMBER HAMMOND: Are we discussing also the OEHHA -- this is the OEHHA findings; is that right? Are we discussing those now too?

CHAIRPERSON FROINES: You can.

PANEL MEMBER HAMMOND: As they're related.

So in that same finding that Gary just mentioned, the range that's given is incorrect. It doesn't agree with Table 15.

CHAIRPERSON FROINES: So the OEHHA?

PANEL MEMBER HAMMOND: Yeah. So they say that for 28 samples they range from .0078 to 1.4 micrograms per cubic meter, but in the table's from 1.004 to 4.56.

CHAIRPERSON FROINES: Yeah, which table are you --

PANEL MEMBER HAMMOND: I'm looking at the OEHHA findings, page 3, at the top of the page, and comparing that to Table 15.

CHAIRPERSON FROINES: In the document?

PANEL MEMBER HAMMOND: In the document. Now, I'm back to the exposure document. I'm just trying to keep these things in sync where I can catch them.

CHAIRPERSON FROINES: I'm just trying to make sure we know where to look, that's all.

PANEL MEMBER HAMMOND: Yes. So if you go to page 15 -- I mean page 38, Table 15. Sorry. So page 38. You'll see that there's an alpha end -- I mean there actually -- there's a 4.56 and a 2.09. So it's just the range.

DPR SENIOR TOXICOLOGIST FRANK: Yes. As soon as we get all of your comments, what we will do as well is sit down with our friends at OEHHA and make sure that both documents have the appropriate numbers.

PANEL MEMBER HAMMOND: Yeah, okay.

CHAIRPERSON FROINES: I'm sorry, Kathy. I'm slow. What document are you --

PANEL MEMBER HAMMOND: All right. Start with the Volume 2, exposure assessment.

CHAIRPERSON FROINES: Yes. Then I'm fine. I know -- I was just looking at the wrong document.

PANEL MEMBER HAMMOND: Page 38.

CHAIRPERSON FROINES: Yeah, got it.

PANEL MEMBER HAMMOND: I do want to make clear that all my comments that -- I mean I keep always making

the critical comments. But this is very good work. So just --

DPR SENIOR TOXICOLOGIST FRANK: Thank you.

PANEL MEMBER HAMMOND: -- just trying a make a good product a little better.

DPR SENIOR TOXICOLOGIST FRANK: Appreciate that.

PANEL MEMBER HAMMOND: And that may cascade into some other areas as well as you do that into the MOEs. I didn't even calculate whether that affects the MOEs.

DPR SENIOR TOXICOLOGIST FRANK: Well, I must admit that we consider your comments very helpful and they actually have allowed us to make a better and more clear document. So we appreciate it.

CHAIRPERSON FROINES: Other comments?

It looks like we've finished this section.

Thank you very much.

DPR SENIOR TOXICOLOGIST FRANK: Thank you, Dr. Froines.

CHAIRPERSON FROINES: The Panel needs to be thinking about as we go through today -- Roger and Kathy have made a number of suggestions and there's been no controversy around DPR's response. So that one of the questions is: Are the changes that are recommended such that we would prefer to have a final look at the document before approval? Or do we approve at this meeting with

the opportunity to look at the document changes and -- because we'll talk about the findings at the next meeting.

PANEL MEMBER BLANC: Well, John, I'm not quite sure about the order that things are going to be discussed in. But isn't the elephant in the room the -- isn't the elephant in the room the difference of world view between OEHHA and DPR as to whether or not when there is a dietary source of exposure that tips the balance of an inhalational exposure which would not otherwise achieve the regulatory threshold for DPR designation under their system? I mean isn't that the major precedence-related issue potentially here?

And so until we struggle with that, I don't think it's possible, unless I don't --

CHAIRPERSON FROINES: No, all I was saying was that's -- this is an issue to keep in the back of your minds as we go through the day.

PANEL MEMBER BLANC: And where will that discussion fall in this?

CHAIRPERSON FROINES: After we're finished.

PANEL MEMBER BLANC: No, I mean where -- at what point do we tart to tackle with that? Do we wait till OEHHA makes their presentation or will it be embedded in the presentation of the risk assessment?

CHAIRPERSON FROINES: I don't know the answer to

that. We'll find out.

PANEL MEMBER BLANC: Well, maybe DPR could tell us where it fits into their presentation.

CHAIRPERSON FROINES: Welcome.

DPR STAFF TOXICOLOGIST SILVA: Thank you. I'm Marilyn Silva from Med Tox, DPR.

PANEL MEMBER FRIEDMAN: Could you move it in closer please.

DPR STAFF TOXICOLOGIST SILVA: Let me just get set up here a second.

CHAIRPERSON FROINES: Okay. Could barely hear you there.

(Thereupon an overhead presentation was Presented as follows.)

DPR STAFF TOXICOLOGIST SILVA: My name is Marilyn Silva from DPR. And I wasn't really sure if I was going to be giving an actual slide presentation today, so I didn't make copies for everyone. But this will be a presentation of the changes suggested by the SRP for endosulfan prior to possible recommendations for listing.

--o0o--

CHAIRPERSON FROINES: You're still too far away from the mike, I'm afraid, for my aging ears.

DPR STAFF TOXICOLOGIST SILVA: And this slide is the slide of my major changes that I made, starting with

cholinesterase, where apparent effects on cholinesterase are inconsistent, occur only at high doses, and are likely secondary to systemic toxicity. A decrease in plasma and RBC, cholinesterase was observed in female rats in the subchronic dietary study, but only at toxic doses of 27 milligrams per kilogram per day.

Endosulfan is a chloride channel blocker in the CNS and shows no direct effect on brain cholinesterase in rats. And I gave the proximate page numbers there, assuming everyone has the same copy.

There was a suggestion that I make more of an emphasis on the neurotoxic effect of endosulfan. The mode of action of endosulfan is to bind and inhibit the GABA receptor chloride ion channel-binding complex, thereby inhibiting GABA-induced chloride flux across membranes. And I added that in several areas.

With regard to biotransformation, stereo-selective endosulfan plus sulfate formation in vitro from human recombinant P-450 showed that alpha endosulfan is mediated by CYP 2B6, CYP 3A4, and CYP 3A5, and the beta isomer by CYP 3A4 and CYP 3A5.

Endosulfan modifies the anti-oxidant enzyme superoxide dismutase, catalase, glutathione peroxidase, glutathione transferase, and glutathione reductase, as well as glutathione in rat liver lung and erythrocytes

when administered via aerosol or in cell cultures, but usually blastoma cells, potentially contributing to anti-oxidant stress in some tissues.

With regard to genotoxicity, I added three more recent genotoxicity studies. And there were wording changes that although there are numerous gene tox studies in the published literature, not all were described, only the studies that were thorough and competently reported.

CHAIRPERSON FROINES: Marilyn?

DPR STAFF TOXICOLOGIST SILVA: Yes.

CHAIRPERSON FROINES: I think I'm the dim bulb of the group today.

The pages 1 through 3 -- I'm looking at the hazard identification risk assessment document. But I don't see the 1 through 3. Am I --

DPR STAFF TOXICOLOGIST SILVA: Pages 1 through 3 should be the summary.

CHAIRPERSON FROINES: What?

PANEL MEMBER BLANC: The Executive Summary.

DPR STAFF TOXICOLOGIST SILVA: No, not the Executive Summary but the summary at the beginning of these.

And what I did for all these page numbers, I wanted it known that they were being added to the summary and eventually the Executive Summary as well as to the

body of the text.

CHAIRPERSON FROINES: So has everybody else found the structures?

DPR STAFF TOXICOLOGIST SILVA: Structure's on page 3.

Now, you know, this is my copy that I printed. I don't know if yours is exactly the same, but I put the structure in.

PANEL MEMBER PLOPPER: Mine starts on page 4.

PANEL MEMBER LANDOLPH: Marilyn, what you e-mailed me was what you're stating now. But I think the other copy of the document didn't have any of that stuff.

DPR STAFF TOXICOLOGIST SILVA: Well, I guess you're missing some pages. But here it is.

PANEL MEMBER HAMMOND: What page is that?

DPR STAFF TOXICOLOGIST SILVA: This is page 3.

PANEL MEMBER LANDOLPH: Marilyn, I think the problem is, what was sent out in November did not -- to all of us did not have those pages. But what you so nicely e-mailed me yesterday does have those pages.

CHAIRPERSON FROINES: Because I don't -- my document starts on page 4.

PANEL MEMBER PLOPPER: Yeah, so does mine.

CHAIRPERSON FROINES: So that we don't have that.

Does this mean that -- on page 35 and 36 is the

discussion about absorption.

DPR STAFF TOXICOLOGIST SILVA: On page 35 and 36?

CHAIRPERSON FROINES: And on 39 and 40 it's inhalation.

DPR STAFF TOXICOLOGIST SILVA: Wait. I have this one.

CHAIRPERSON FROINES: Oh, here there is some -- yeah, there is some metabolism data on 40.

DPR STAFF TOXICOLOGIST SILVA: On 39 under "inhalation" is a study that describes an inhalation exposure where various catalasa -- or actually dismutase --

PANEL MEMBER HAMMOND: Can you say exactly where --

DPR STAFF TOXICOLOGIST SILVA: Page 40, it's 1, 2 -- third paragraph -- oh, talks about the P-450s.

CHAIRPERSON FROINES: Yeah, I see that. But 35 and 36 doesn't -- as far as I can see, doesn't have any --

PANEL MEMBER BLANC: I think, John, the problem is that there was a later revision to the document which is not -- was not circulated to the Panel.

CHAIRPERSON FROINES: Is that correct?

PANEL MEMBER LANDOLPH: John?

DPR STAFF TOXICOLOGIST SILVA: Oh, I think part of the --

CHAIRPERSON FROINES: Because I have a letter dated November 16th that had all these documents.

DPR STAFF TOXICOLOGIST SILVA: These two studies -- the study on page 36 is the Chan, et al. And I just made some changes about the -- in another biotransformation assay on page 35 by Dorough, 1978.

CHAIRPERSON FROINES: So this document that I have has the metabolic pathway it appears on page 42.

DPR STAFF TOXICOLOGIST SILVA: Right. It should be the same one. There were -- the heading -- for some reason these didn't end up on the same page they were supposed to. But the heading on the previous page has all the enzymes added -- the metabolic enzymes added.

CHAIRPERSON FROINES: I've always worried about this. We've got this big double bond sitting there in endosulfan. And it's possible you're also going to have another pathway which is forming of the epoxide. And I don't know if there are any studies that have looked for products of the epoxide or the diol that would result from epoxide hydrolase. I assume that -- I'm assuming that there are no studies that have looked at that.

DPR STAFF TOXICOLOGIST SILVA: No, I didn't see specifically epoxide hydrolase used for that.

CHAIRPERSON FROINES: No, till you get the epoxide first.

DPR STAFF TOXICOLOGIST SILVA: Yeah, I did not see that intermediate or the use of epoxide hydrolase.

CHAIRPERSON FROINES: Yeah, I think this metabolism is actually much more complicated than this. But it's more a lack of data to look at it.

So go ahead. Don't let me hold you up.

DPR STAFF TOXICOLOGIST SILVA: Okay. Further clarification of endosulfan's lack of oncogenicity was added. Neither in FIFRA guidelines acceptable animal studies nor in open literature was endosulfan found to be oncogenic. There were inconclusive findings from contradictory results of genotoxicity induced by endosulfan technical as measured by gene mutation, chromosomal aberration, and other genotoxic effects, tests and studies submitted to DPR and those found in open literature. And also endosulfan is categorized as an A4, not classifiable as a human carcinogen, by the American Conference of Governmental Industrial Hygienists.

CHAIRPERSON FROINES: Do you want to ask questions now, Joe?

PANEL MEMBER LANDOLPH: Yeah, for Marilyn.

DPR STAFF TOXICOLOGIST SILVA: And let me say that I -- we really struggled with the wording, but we are totally open to any suggestions.

PANEL MEMBER LANDOLPH: Well, I think with regard

to the genotoxicity, I probably reiterate most of the comments I made and Dr. Froines made last time. If you look at those very nice tables summarizing the data you have, for instance, in the Ames assays there's a lot of negatives, but then there's a few assays that are positive. So that doesn't mean that it's negative. It doesn't mean it's inconclusive. What it means is if you look at the spectrum of mutations that are allowed to be formed, it doesn't make these lesions but it makes these lesions. So it really is positive.

And as you point out in your summary, it causes -- endosulfan causes DNA adducts, DNA damaged by the common assay, chromosomal aberrations, and there's three -- all the bone marrow studies are positive. So to me that's a significant amount of gene tox data. So I would not call that inconclusive.

OEHHA's wording I think is a little bit more appropriate -- say a lot more appropriate, where you could say that it's negative in certain standard tests but that it's positive in causing DNA adducts, DNA damage, bone marrow positives and point out the other positives. I think it is genotoxic. And I would request that you please alter that wording, both in the summary here and in the Executive Summary. It doesn't appear at all. I think you should please put some gene tox summary there.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: I had something along those lines. I was a little concerned. I'm not sure where I read it, but they were saying that this did not produce cancer in experimental animals. But then there was a sentence that said, "But later on somebody reinterpreted those slides and did find that the cancers were being produced." And then the next sentence says, "We conclude there's no carcinogenicity."

DPR STAFF TOXICOLOGIST SILVA: No, that -- I don't think that was mine. That was a study done in 1978 by Powers. And that was the group that were -- they were testing hundreds of pesticides and chemicals for carcinogenicity. They tested rats and mice. And the study that was being referred to was in rats. And there was a huge amount of mortality.

And the person who reinterpreted the slides, there's no description at all of how it was read, if it was impartial. He was doing the reading. And generally under the pathology working group, you have at least three different labs -- independent labs looking over the same slides, you know, double blinded. But this person, you know, he didn't talk about his methods and --

PANEL MEMBER FRIEDMAN: I think it would be very good if you could -- maybe it is in the full report. But

what I read, it would be good if you explained why you didn't take it real seriously. Because here it says, "It was reinterpreted cancer was found. We conclude there's no cancer." It seemed to me like a non sequitur.

DPR STAFF TOXICOLOGIST SILVA: Well, okay, okay.

PANEL MEMBER FRIEDMAN: But I think, you know, the doubts you express are very important, very valid, and they should be in there.

CHAIRPERSON FROINES: I have a question about that as well that I'm confused about and Melanie or George can address, I think.

In the OEHHA document on the same topic, OEHHA says, "A reanalysis of pathology slides from the two National Cancer Institute studies of 1978 suggested that both were positive for carcinogenicity." Well, that's a pretty strong statement. And then OEHHA says, "Based on all the above information, we find there is insufficient evidence to suggest endosulfan is carcinogenic." Well, your sentence before that says that the reanalysis says it is carcinogenic and then you follow up that sentence and say it's not carcinogenic.

So I think there is a contradiction. And I think that it could be solved by saying that -- you can say there's insufficient to suggest endosulfan is carcinogenic. But since there was some ambiguity, further

investigation needs to occur on this compound.

DPR STAFF TOXICOLOGIST SILVA: Okay. We strongly disagree with that, because a later test was -- let's see.

The mortality was so high -- they used only two treatment levels. The mortality was so high that it precluded any useful oncogenicity data. And there was also no analysis of the treatment material, so we don't even really know what they were getting.

CHAIRPERSON FROINES: All I'm saying -- all I was saying is I was suggesting -- that you say there's insufficient evidence. I didn't quarrel with that. But I said that I -- if I make an epoxide on that compound with that double bond, it's going to bind -- it's going to form an electrophilic bond with DNA. So there is a mechanistic basis to -- and there is inadequate evidence on an epoxide formation. But if there is epoxide formation, then you've got a perfect situation. And that would explain DNA adducts. I mean there is -- there are DNA adducts, and that we know. And that's an important finding. That shows that there's some electrophilic site in endosulfan that is capable of binding with DNA.

Now, if you don't get complete DNA repair before the cell turns over, you're going to have a mutagenicity. And we've already agreed that it looks like this stuff is mutagenic. And so that doesn't guarantee that it goes on

to produce cancer. We know that.

But all I'm saying -- I wouldn't disagree so strongly. I would simply say that further studies in the future on endosulfan carcinogenicity would be reasonable.

Who can -- I'm an academic. I'm always interested in more research.

DPR STAFF TOXICOLOGIST SILVA: I can't agree because -- well, there's been the one-year dog and the two-year rat. And this 1978 study had so many problems. I mean I could spell those out in greater detail in the --

CHAIRPERSON FROINES: But the fact that you get a couple negative studies doesn't mean that the compound is negative. It depends -- we're not -- a one-year dog study isn't an adequate study.

DPR STAFF TOXICOLOGIST SILVA: Well --

CHAIRPERSON FROINES: I mean a one-year dog study, you're studying a puppy. So you're looking at early life carcinogenicity.

A two-year rat study is certainly reasonable.

But I'm going on what OEHHA says here, that a reanalysis of pathology slides from the two studies suggested that they were both positive for carcinogenicity.

So all I'm asking is to say further investigation is reasonable. Nobody can disagree with that.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Hi. This George Alexeeff. Yeah, we'll make that clarification.

And part of our -- we felt it was important to mention this reanalysis. At the same time whenever there is a reanalysis of slides, I don't know, I guess we sort of take it with a little bit of a grain of salt, unless the reanalysis sort of leads to a rethinking of all the information. Because the reanalysis is usually done with an informed -- on an informed sort of basis, as opposed to the original study where you are not sure what the result is going to be. So there were some questions, as Marilyn mentioned, in terms of the study design and such. So we felt it was important to mention, but it wasn't convincing to us.

So we'll add that clarification as to why we kind of made that sort of leap of statement.

CHAIRPERSON FROINES: Let me just reiterate a point I want to make.

In the 1970s when all this got going, and in the early 1980s, EPA put out a document that showed there were a hundred in vitro tests that could be used for looking at mutagenicity. So we had a hundred tests. And we later found out that they simply measured the same kinds of endpoints, a lot of them. And so they were just tests. They were individual tests, that all were in a sense

originally seen as separate from one another.

Now, we think about things differently because we think about mechanism. And if you have a study that shows DNA adducts are formed, then you have to say there is a potential for that to be carcinogenic based on mechanism. And so it's a different process. It's not looking at in vitro tests as individual little marker tests saying if you've got 17 that are positive and 3 that are negative, you conclude it's -- I mean there's no discussion about criteria. We ought to have a discussions at some point about criteria for determining what's positive and what's not. Because in this case, you have a lot of positive tests that Joe's pointed out. But then DPR says it's not genotoxic. Well, we fundamentally disagree with that.

DPR STAFF TOXICOLOGIST SILVA: No, we didn't.

CHAIRPERSON FROINES: What?

DPR STAFF TOXICOLOGIST SILVA: We changed our wording.

CHAIRPERSON FROINES: Yeah. So I'm saying that if it's genotoxic, it has the potential mechanistically for carcinogenicity. And so all I'm saying is putting in one sentence that says we should look further into the fact that there is genotoxicity and there was some positive results from the NCI studies seems to me to be -- I mean it's a sentence.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Agreed.

George Alexeeff. That sounds fine to us.

CHAIRPERSON FROINES: So, Marilyn, I think -- I don't know why you would say you disagree so strongly.

DPR STAFF TOXICOLOGIST SILVA: I disagree strongly because the person who reanalyzed the slides, it was done so poorly, with absolutely no controls at all. And so it makes me highly suspicious, especially when the mortality is so high and there is not a sufficient test for oncogenicity.

CHAIRPERSON FROINES: But you're missing my point. My point was that there is evidence -- there's evidence of genotoxicity and, therefore, carcinogenicity should be studied --

PANEL MEMBER BLANC: John, maybe --

CHAIRPERSON FROINES: -- by definition.

PANEL MEMBER BLANC: -- maybe we should take a break. We're at that sort of 90-minute --

CHAIRPERSON FROINES: Just a second.

No, I don't want to --

PANEL MEMBER LANDOLPH: Yeah, I would support John's statements. I feel the same way. I think there is certainly genotoxicity.

In addition, there is inhibition of gap junctional communication, which you pointed out nicely in

your report, which is very much what PCBs do. So on the one hand you have genotoxicity and you have gap junctional communication inhibition, which is an attribute of carcinogens. So we're not saying you can say this is carcinogenic. That's not what we're saying. But we're saying, based on these properties, it should certainly be studied further and conclusive carcinogenicity studies done in the future to put this issue to rest one way or another, because there is suspicion that it might be based on genotoxicity and inhibition of gap junctional communication.

And it's an important issue which needs to be resolved. Because if it's positive, then that knocks the dose response curve orders of magnitude down further than where it is now. Then it would change the whole regulation.

So I think that issue should be mentioned.

CHAIRPERSON FROINES: I mean I think this is almost an academic discussion, because hopefully endosulfan will disappear in a few years. It's obviously disappeared in most of the -- many countries in the world. And so we're still in the sort of prehistoric period where we keep thinking about standards, when Saudi Arabia has banned it.

So that it may be that endosulfan isn't a high

priority chemical over time. But still given the genotoxicity information seen mechanistically and -- I'm just repeating myself, so I'll stop.

All right. Why don't we take a break and then we'll go on with the rest of the presentation.

(Thereupon a recess was taken.)

CHAIRPERSON FROINES: I think Tobi and I have talked through an issue, and so I'm comfortable. But I'm sure that others aren't comfortable. So let's ask Marilyn to hold for a second and just clarify -- Joe told me at the break that the document that he saw was not -- and correct me if I'm misstating this -- the document that he saw was not the document that we have here. And so the problem is: How can we evaluate a document that we have here if there is another document? And Tobi said that there really isn't another document. But Joe gave me the impression that Marilyn was working on sections over the weekend. So that if there are changes, we don't -- we don't have that.

So we need to sort of figure out what is it. Because we can't very easily evaluate a document for which -- if there are sections missing or there is another version even, which I doubt that it would be the stuff that Marilyn was working on.

So is that a correct statement, Joe?

PANEL MEMBER LANDOLPH: Well, Marilyn very kindly sent me a document which was nicely outlined in yellow. And it looks different to me, because you mentioned you were missing the first four pages, and they're all here and the figures are here. It's very nice. And it's outlined in yellow.

Do you have that?

CHAIRPERSON FROINES: No.

DPR STAFF TOXICOLOGIST SILVA: When we were e-mailing on Sunday, what I was working on actually was my presentation, not my document. But I did change -- or make it a little more clear the statement about DPR's recommendation for consideration of endosulfan listing as a TAC since I was working with Joe on those. And then I made a few very small changes in the endocrine disrupter area. But there's nothing major. I mean it's not like a whole new section or a whole new major anything. I was working on my presentation over the weekend.

CHAIRPERSON FROINES: So what I hear you saying is there are some small changes around a couple of subjects, but basically the document we have is the complete document?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER BLANC: How is that possible?

PANEL MEMBER LANDOLPH: You're missing the first

three pages still.

CHAIRPERSON FROINES: We're missing the first three pages. And we have the metabolism in page 40 or something.

PANEL MEMBER HAMMOND: I downloaded that document you have there, John, from the web.

Does the web -- is the web version that was up yesterday, is that the latest version?

DPR STAFF TOXICOLOGIST SILVA: (Nods head.)

PANEL MEMBER HAMMOND: But that's different than the version that was mailed to us; is that correct?

DPR STAFF TOXICOLOGIST SILVA: No, that's the same version you got.

PANEL MEMBER HAMMOND: In the mail?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER HAMMOND: Okay.

DPR STAFF TOXICOLOGIST SILVA: The issue was --

PANEL MEMBER HAMMOND: That does have pages 1, 2, and 3, but --

DPR STAFF TOXICOLOGIST SILVA: The issue -- I don't know. Well, it should have everything.

CHAIRPERSON FROINES: Yeah, it does.

PANEL MEMBER HAMMOND: So what was put on the web was identical to what was mailed to us?

CHAIRPERSON FROINES: No.

PANEL MEMBER HAMMOND: That's what I'm trying to find out.

CHAIRPERSON FROINES: Because this is your document --

PANEL MEMBER HAMMOND: She's saying yes.

CHAIRPERSON FROINES: -- that was downloaded. And this has the metabolism on page 3, as you point out up here. And that's not the case in the document that was mailed to us.

PANEL MEMBER BLANC: Well, somebody must have been in charge of mailing the document. This is not something that I think is fair to our panel to have to spend 15 minutes figuring out. There's got to be somebody at the Department of Pesticide Regulation who mailed the document and who knows whether what they mailed was the final version or not, and somebody else who put out the document on the web. This should be easy enough to figure out.

And I have to say that I'm not amused if in fact the case is that there is a final document on the web, that that's not what we were sent by mail.

DPR STAFF TOXICOLOGIST SILVA: The final document on the web as far as I know is what you received.

CHAIRPERSON FROINES: Well, the final document on the web --

PANEL MEMBER HAMMOND: We couldn't hear you. Could you speak in the microphone.

CHAIRPERSON FROINES: -- is different than the document we were mailed.

DPR ASSISTANT DIRECTOR JONES: This is Tobi Jones.

And I'd have to point to another colleague with regard to Paul's particular point. The document that you received is missing the first three pages of Volume 1. I apologize for that. I can't explain how that happened.

The document you received on paper does not have the Executive Summary that is on the web. And those are the differences.

So I apologize for the error, and we'll --

CHAIRPERSON FROINES: And some -- she said endocrine disruption discussion and what else?

DPR ASSISTANT DIRECTOR JONES: Well, I think in not knowing whether or not we would be making presentations today, I believe Marilyn was trying to prepare for issues that the Panel may have. And she was also in dialogue with Dr. Landolph over his issues.

CHAIRPERSON FROINES: I was about to say I think we can proceed. But Joe is going through some comparison, so I'll hold for just a second.

PANEL MEMBER LANDOLPH: That's okay. Page 20

there's an extra statement about bystanders that was in the new document that was not in the one sent earlier.

PANEL MEMBER HAMMOND: Joe, can you use the mike.

PANEL MEMBER LANDOLPH: Yeah. On page 20 there's an extra statement about bystanders that was in the version you and I pulled that Marilyn sent us that was not in the old document.

PANEL MEMBER BYUS: I'm now very confused.

(Laughter.)

PANEL MEMBER BYUS: Not that I wasn't earlier.

But particularly about the Executive Summary, what Executive Summary are we looking at here that was handed out to us this morning?

CHAIRPERSON FROINES: The one that was given to us today.

PANEL MEMBER BYUS: Right. So that is the Executive Summary that is in the web and was mailed to us --

DPR STAFF TOXICOLOGIST SILVA: It was not mailed to you.

PANEL MEMBER BYUS: It was not mailed. All right.

So this is the first time we've seen it. It's here today. And this is the one -- so this is the Executive Summary as you intend to publish it or add it to

the document; is that correct?

CHAIRPERSON FROINES: Yes.

PANEL MEMBER HAMMOND: And this has been on the web for how long? Has this been on the web?

DPR STAFF TOXICOLOGIST SILVA: I'm not really sure how long it's been on the web.

PANEL MEMBER BLANC: Well, John, as a process, again consistent with our earlier discussion, what I would suggest is that we hear out the remainder of the comments, in particular what I suspect is a major potential issue related to the difference between OEHHA and DPR, and then we look at the constellation of issues to try to get at the point that you wanted us to keep in the back of our mind as to how it is best to proceed today.

CHAIRPERSON FROINES: Yeah, I have a slightly different view of that now. But we'll talk about it later.

So, Marilyn, why don't you -- hearing no objection to what Paul said, we'll follow that, and -- so let's go ahead.

DPR STAFF TOXICOLOGIST SILVA: Okay. So then the next section that I worked on was the lack of support for additional safety factors for infants and children. And I have these pages listed and I also have a presentation.

And then finally DPR's statement about

recommending endosulfan for listing as a toxic air contaminant note that since both the bystander scenarios have MOEs of less than a thousand, DPR recommends that endosulfan be listed as a potential toxic air contaminant.

And I also did change the -- instead of just writing TAC 2002, which is the act, I put it -- I changed the reference to the California Food and Ag Code. And that was done -- the Food and Ag Code was done since you got your draft.

CHAIRPERSON FROINES: And OEHHA agrees with the endpoint? That was my recollection.

DPR STAFF TOXICOLOGIST SILVA: Yes, there's no question about the endpoint. It's just the safety factor.

CHAIRPERSON FROINES: Are there differences of opinion between the two agencies on the safety factor issue?

DPR STAFF TOXICOLOGIST SILVA: Yes. And I don't know if everyone got the OEHHA findings, but I have a presentation about our interpretation.

CHAIRPERSON FROINES: Melanie or George or Andy, somebody -- why don't you go ahead and give your perspective and then OEHHA can respond.

We need the attention of the lead at least, and Dr. Blanc would be helpful too. And we can look at document problems later.

--o0o--

DPR STAFF TOXICOLOGIST SILVA: Okay. I wanted to summarize or mainly discuss the lack of support for additional uncertainty for factors for young animals due to possible increased sensitivity.

CHAIRPERSON FROINES: Could you put the mike a little closer. I'm sorry.

DPR STAFF TOXICOLOGIST SILVA: Specifically with regard to the subchronic inhalation NOEL, as a review here are the definitive studies selected for the critical NOELs for each scenario.

And you can see that for the -- the acute rabbit developmental we're using as the dietary, the subchronic rat reproduction with a NOEL of 1.18 for systemic effects we're using for the subchronic oral, and for the chronic we're using the one-year dog with a NOEL of 0.57 based on neurotoxicity. For the acute and the subchronic we're using the 21-day inhalation with a NOEL of 0.194. And for the chronic we're using a conversion factor, an extra uncertainty factor of 10 to make a NOEL of 0.194.

CHAIRPERSON FROINES: Could you go back for just a second.

DPR STAFF TOXICOLOGIST SILVA: Oh, sure.

CHAIRPERSON FROINES: I don't quite understand the uncertainty sub for chronic ratios.

DPR STAFF TOXICOLOGIST SILVA: To get an equivalent or an estimated chronic NOEL, you divide it by 10 to -- what is the word? -- extrapolate from subchronic to chronic.

CHAIRPERSON FROINES: And So your total uncertainty factor's a thousand?

DPR STAFF TOXICOLOGIST SILVA: Right. Yes.

CHAIRPERSON FROINES: Okay. Thank you.

--o0o--

DPR STAFF TOXICOLOGIST SILVA: I would like to show that there's sufficient evidence based on available toxicity studies to show that no additional uncertainty factors needed to address neurotoxic or reproductive effect concerns in young animals.

--o0o--

DPR STAFF TOXICOLOGIST SILVA: Comparison of subchronic neurotoxicity NOELs in young rats. Mainly we'll start with the neurotoxicity issue. For the developmental neurotoxicity, which was the one that we've been waiting for, the animals were treated from gestation day 6 through lactation date. Thirty dams per dose were used and ten pups per sex per dose were assayed and observed postnatal day 21 and 75 for the neurotoxicity battery.

The NOEL for that study, and it was a dietary

study, was greater than 29.8, the highest dose tested.

An IP study was used. And it was suggested by OEHHA that the IP would suffice in lieu of an inhalation study.

In these next two studies, males were treated from day 1 of birth to two, three, and five weeks, with eight animals per dose. And there were some neurotoxicity effects at one milligram per kilogram per day with a NOEL of 0.5.

Another study -- and these are both IP studies -- animals were treated day 1 postnatally, both sexes, the sex was not distinguished in the study, for three to five weeks with an eight-day recovery. And there were four pups per sex per dose. They were -- there were effects at 1 milligram per kilogram per day with a NOEL of 0.5.

And the adult inhalation NOEL for the -- the adult inhalation NOEL is actually lower than that of the young animals' subchronic inhalation NOEL of 0.194.

--o0o--

DPR STAFF TOXICOLOGIST SILVA: The weight of evidence indicates there's no increased sensitivity in fetuses, neonates, or pups of either sex. Endosulfan also has no effect on fertility.

The yellow studies -- or these -- actually it turns out green here -- are studies from the Industrial

Toxicology Lab Center in India and from the open literature. These studies here are all FIFRA guideline studies. And this one here is a study from China. The green here shows the lack -- a weight of evidence for the lack of repro or fertility effects.

If you look at the NOELs in this column, you'll see Sinha, et al., here with a LOEL of 2.5. And this is flagging a possible effect in the animals.

This was performed on three-week-old weanling pups, that were observed for 90 days, by gavage. And there were five pups per dose.

In the next study with a lower LOEL, the animals were treated from gestation day 12 through birth. And they were cross-fostered until day 21 -- postnatal day 21. But in this study, there were only three dams treated. And the dams were the treatment unit, and yet the pup data were reported individually and not on a per-litter basis. So the effect that we're seeing, it's not known if that's occurring in only one litter. So that study is in question.

In this study there's no effect on testes weights. In this study testes weights are decreased.

Another study by Dalsenter, et al., treated animals from gestation day 15 through day 22, with observations through postnatal day 65 and 140.

And in this there were slightly higher treatment groups. And at postnatal day 65 there were effects seen. So the LOEL was 1.5. But there were no longer effects by day 140. So the NOEL was greater than 1.5. And in this study, the testes weights were slightly increased.

CHAIRPERSON FROINES: Why is the NOEL greater than 1.5?

DPR STAFF TOXICOLOGIST SILVA: That was the highest dose tested, I think. Well, maybe I'm --

CHAIRPERSON FROINES: I thought you said there was -- that that was a LOEL --

DPR STAFF TOXICOLOGIST SILVA: Well, at day 65 that was the LOEL because effects were seen on day 65. But by day 140 no effects were seen.

PANEL MEMBER BLANC: No reproductive effects?

DPR STAFF TOXICOLOGIST SILVA: Right, no reproductive effects.

PANEL MEMBER BLANC: And by reproductive effects, you mean decreased litter size or something?

DPR STAFF TOXICOLOGIST SILVA: No, I'm talking about sperm counts, sperm motility, morphology, testes weights, prostate weight.

PANEL MEMBER BLANC: I see.

Well, can I just ask a small theoretical question or public policy question. I'm not sure what it would be.

But if you have a period of time when there are reproductive effects, then does it matter that at some later period of time there aren't reproductive effects? I mean if there is a period in which there are reproductive effects, then it's reproductive toxic, isn't it?

DPR STAFF TOXICOLOGIST SILVA: Well, the thing is that you want to see what the bottom line is as far as effects that -- the question is: Is effects that occur in -- during gestation and perinatally, are they going to be manifest in the adult animals?

PANEL MEMBER BLANC: I see. Okay.

DPR STAFF TOXICOLOGIST SILVA: And so I think that this is very important.

Now, the same lab did a study where they treated 21 days pre-mating using eight pups per dose -- eight male pups. When I'm talking about pups, it's male pups. And they found no -- no repro effects at greater than 1.5, which is the highest dose tested. And the NOEL for the study was greater than 1.5.

And with Nye, this was the study that I selected for my oral endpoint study for acute -- my acute NOEL. And while there were neurotoxic effects in the dams at 0.7, there were no effects in the pups or the fetuses at greater than 1.5. And this was the highest dose tested. And they used 26 dams for per dose.

Fung was -- the Fung study was Sprague-Dawley rats. And those animals were treated from gestation day 6 through 19. And they had 28 dams per dose. And fetal -- and dam effects were seen at 6, which is a very high dose, and it was very toxic to the dams. And the fetal and dam NOEL was both 2.

In the Edwards study, which is our two generation -- well, this study would be the one that would show if there were effects occurring prenatally, during gestation, lactation, and pubertal. It would be manifested in this study, because this study -- there were two generations with two litters per generation. And there were 28 to 30 per sex per dose per generation. And there were no repro effects at the highest dose tested in either sex where the NOEL was 1.18 based on systemic effects.

--o0o--

DPR STAFF TOXICOLOGIST SILVA: And Gilmore was the developmental neurotoxicity study. And this was also a diet study. Twenty-three litters. And since this was mainly meant to be a neurotoxicity study, that was the main endpoint.

But since -- in this reproduction study, since it was an old study, they did not look at sperm motility, morphology, or sperm count. And this was all done in

this -- in the Gilmore study to make up for that.

So in that study there were no repro effects at 29.8, which is the highest dose tested. And the pup LOEL, however, was based on body weight of approximately 5 percent at less than 3.74, which is the lowest dose tested.

The paper buy Zhu treated the animals through gestation to postnatal day 28 using ten males per dose, and -- or examining ten males per dose. And there were no repro effects at all at 2.5 -- greater than 2.5, which was the highest dose tested. And I would like to compare that to our acute and subchronic inhalation NOEL of 0.194.

--o0o--

CHAIRPERSON FROINES: Well, I want to make a comment -- go back now. I want to make a comment.

The one thing that's clear about reproductive and -- but particularly both developmental and reproductive studies in the literature is that there are enormous strain differences in outcome. And that I could show you tables where people compared strains for various -- various chemicals, and what you see is -- in some strains you get zero and some strains you get high percentages and so on and so forth. So that there is a strain issue here, I think. It looks to me like the Wistar rat is less susceptible than the Druckrey rat. And

so that you have a potential issue of these studies here are giving you lower values; and then when you get to the Wistar rats, you get -- with the exception of this issue that Paul raised, you get relatively high numbers.

And so for -- the problem with weight of evidence is that you -- if you weight every strain the same, you're not really addressing the differences that occur among strains. And so you can't -- you can't take -- it's like taking a mouse and a rat and saying that you should see similar results in both. Obviously there are interspecies and intra-species issues.

Are these all industry studies here?

DPR STAFF TOXICOLOGIST SILVA: Yes.

CHAIRPERSON FROINES: So these are industry studies and these are academic studies?

DPR STAFF TOXICOLOGIST SILVA: Right, including the bottom one.

CHAIRPERSON FROINES: Yeah. So this gives you -- this gives you a NOEL of .1 milligram per kilogram per day?

DPR STAFF TOXICOLOGIST SILVA: A LOEL with three dams. But, as I said, we don't know if all the effects were occurring in one litter because it was not reported on a per-litter basis. All the studies in blue individual data were available.

CHAIRPERSON FROINES: Well, let me say that I'm not necessarily surprised that your -- that this pattern is occurring. And I think one has to be careful about this interpretation, because, yes, there's a problem perhaps with the -- with the numbers, but it's not -- but one still has to look at positive studies.

Paul.

PANEL MEMBER BLANC: Can I -- Paul Blanc here. I just want to clarify something.

You were showing these data, if I understood it correctly, in order to assess whether or not the factor of 100 was reasonable also to use for reproductive and neurotoxic effects, or whether there was any evidence that neurotoxic and reproductive effects were even more sensitive and therefore a safety factor might have to be a thousand and not a hundred.

DPR STAFF TOXICOLOGIST SILVA: No, that's -- I think that you're referring to the FQPA. That's relating to dietary. And this is strictly having to do with OEHHA's issues about the inhalation.

PANEL MEMBER BLANC: And can you again clarify for me then. The point that you're trying to make with your analysis of these studies is whether or not the inhalation NOEL was sufficiently conservative or not?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER BLANC: And in order to support that argument you were trying to show that the NOELs that you would arrive at with these studies were not substantively lower; is that correct?

DPR STAFF TOXICOLOGIST SILVA: Right, that the -- that even if you did take a factor of 3, and often 10 even, you're still well within protective doses for our inhalation NOEL that we've selected.

PANEL MEMBER BLANC: And the inhalation NOEL of .194 already has built into it a factor of 100 --

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER BLANC: -- from animal data, is that correct, because you're going from species and then to a more sensitive subgroup within --

DPR STAFF TOXICOLOGIST SILVA: That's right.

PANEL MEMBER BLANC: Is that right?

DPR STAFF TOXICOLOGIST SILVA: That's right.

PANEL MEMBER BLANC: So if -- to come back to John's point then, I just want to make sure I understand your reasoning. If you take the LOEL of one milligram per kilogram per day, which is the LOEL on that species, and you used a factor of 10 to get to an extrapolated NOEL, as John indicated, that would be .1 milligram, which would be slightly lower than the .194, but actually the .194 has a factor -- already includes a factor of 100 going across

species which is not here, so you'd have to go down another 10 from to .194 to .0194 -- I'm sorry -- to .01, right, from .1 to -- would be the NOEL, and then across species it would be .01; is that correct?

DPR STAFF TOXICOLOGIST SILVA: We would divide 0.194 by 100.

PANEL MEMBER BLANC: No, no. I mean does the one milligram in the green --

DPR STAFF TOXICOLOGIST SILVA: To go -- that would be a hundred also, interspecies, intra-species.

PANEL MEMBER BLANC: So it would be .001?

CHAIRPERSON FROINES: Yes.

PANEL MEMBER BLANC: And wouldn't .001 be considerably less than .194 in milligrams per kilogram per day?

DPR STAFF TOXICOLOGIST SILVA: Well, you would be .00194.

PANEL MEMBER BLANC: No, I'm not talking about the bottom here. I'm talking about comparing -- you're comparing -- I just want to make sure I understood what you were doing.

DPR STAFF TOXICOLOGIST SILVA: I don't understand what your question is.

PANEL MEMBER BLANC: All right. Let me try to clarify it again.

You presented these data in order to show -- in order to address the point: Is the .194 from the inhalation data sufficiently conservative enough?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER BLANC: And so therefore you looked at these data to see, "Well, if I look at these data, am I having any signals that things would be more sensitive using these other endpoints," is that correct?

DPR STAFF TOXICOLOGIST SILVA: Right.

PANEL MEMBER BLANC: Okay. So you have this LOEL of one milligram per kilogram per day. But if you converted that LOEL to be comparable to the .194, you'd have to divide it by 100, right, because you'd have to --

CHAIRPERSON FROINES: A thousand.

PANEL MEMBER BLANC: -- a thousand because you'd have to get first to a NOEL and then do the same cross-species division that led you to the .194. And wouldn't that give you a value that was considerably lower? And so if the point is that there is no signal here -- did I miss something or is my question still too confusing?

DPR STAFF TOXICOLOGIST SILVA: Yeah, I still don't understand.

PANEL MEMBER BLANC: Is there someone who can help?

CHAIRPERSON FROINES: I can. If you took that study that -- the Sinha study, you would end up with a NOEL of -- you would end up with a value of .001.

PANEL MEMBER HAMMOND: And would that account for the dietary versus inhalation as well? Because there's evidence that inhalation is effective at a lower concentration -- lower dose.

DPR STAFF TOXICOLOGIST SILVA: Yeah, I think you are misunderstanding.

PANEL MEMBER BLANC: Okay. So can you clarify for me.

DPR STAFF TOXICOLOGIST SILVA: Because you take the NOEL and divide it --

PANEL MEMBER HAMMOND: No, a LOEL.

DPR SENIOR TOXICOLOGIST FRANK: This is Joe Frank again from DPR.

Actually with the LOEL, you were correct. When you do an adjustment to an adjusted NOEL, you would do a factor of 10. So that would be .1. That is actually what you compared to the NOEL down here on inhalation, because when you put in the other factors, the species-to-species variability, all of those are done to the NOELs. So the two comparisons -- if you really want to compare that study on top to the inhalation study, you just compare the NOELs. And the NOEL on the second study down would be .1.

CHAIRPERSON FROINES: So we're talking about a comparison of .1 to --

DPR SENIOR TOXICOLOGIST FRANK: -- .194.

CHAIRPERSON FROINES: -- to .194.

DPR SENIOR TOXICOLOGIST FRANK: Yes, sir.

PANEL MEMBER HAMMOND: What about the other data? I may have misunderstood the other data, that in other places there was evidence that inhalation was -- a lower dose of inhalation would achieve the same effect as a dietary dose? And this would run counter to that in that case.

DPR STAFF TOXICOLOGIST SILVA: Well some -- why would that -- oh, well, the pups once again have higher -- I don't understand your question.

PANEL MEMBER HAMMOND: I thought I had read in this material that you had said -- and I may have gotten this wrong -- that for the same dose given in a dietary manner and at the same dose given by inhalation, that the inhalation dose was much more effective because of the first pass.

DPR STAFF TOXICOLOGIST SILVA: Well, even if you had -- even if you took 50 percent by the first pass of the liver or whatever, you're going to get .25 by this IP study and even much higher. So the .194 is --

PANEL MEMBER HAMMOND: Is this a -- I'm

forgetting now. Is this a study that was done by inhalation or a study that was done by diet and adjusted for inhalation?

DPR STAFF TOXICOLOGIST SILVA: The first study was done by diet and the second study was done by IP, the second two studies.

PANEL MEMBER HAMMOND: And then you adjusted it for inhalation?

DPR STAFF TOXICOLOGIST SILVA: Well, I didn't make any adjustment, because there are some studies that are -- that are performed by IP where inhalation can't be done. So often times it's a substitute.

CHAIRPERSON FROINES: I have some problem with -- what is "in lieu of inhalation" meaning?

DPR STAFF TOXICOLOGIST SILVA: Well, in place of the lack of an inhalation study there's the IP subchronic study.

CHAIRPERSON FROINES: Yeah. I would assume that an inhalation study would give you a greater internal dose.

DPR STAFF TOXICOLOGIST SILVA: Well, I agree. I agree, especially since IP goes right in to the portal circulatory system.

CHAIRPERSON FROINES: Right.

DPR STAFF TOXICOLOGIST SILVA: But this is what

we have, and this was one of the studies OEHHA used for an example.

Another thing about this study is that the LOEL was 1 for the pups and compared in their document to 3 in the adult as a 1-to-3 ratio for more sensitivity to pups. However, in that study, the dams -- the adults, males and females, were only treated at 3 on a subchronic basis. They were not treated at any lower doses. So it's not really a comparison of like doses for like treatment times.

CHAIRPERSON FROINES: So can we go ask George and colleague.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Hello. This is George Alexeeff from OEHHA. And with me is Dr. Charles Vidair, who is our lead toxicologist in our Pesticide and Food Toxicology section.

And we also looked at this -- the whole data set very carefully. And I'll just give you a couple points and Dr. Vidair can show a couple of slides summarizing some of our issues here.

We've tried to lay it out in our revised findings what the issues were. It comes down to issues of we feel there's still is uncertainty with regards to pharmacokinetics and reproductive toxicity.

If I can step back a little bit further. In 2001

we brought our prioritization document prioritizing chemicals for protection of infants and children. And in that, we identified those areas are the types of studies that we felt infants and children are likely to be more sensitive.

And it included, you know, developmental toxicity, and neurotoxicity, endocrine disruption, immunotox, respiratory, genotox, and carcinogenicity. Those were studies that we kind of identified as things that, if we saw those studies, then we would think that it's possible infants and children might be more sensitive than adult animals.

So we were trying to look at this whole data set from that mind set, because -- so when we say -- another statement is when we look at all the reproductive toxicity and developmental toxicity data, we see the pattern of information is, when you look at the studies carefully, is what you'd expect. Because the studies that are negative, we feel they're negative because of differences of timing of when the analyzed or what they looked for. So we feel some of the studies they didn't find things is because they didn't look at the studies that found effects. So we think that the studies are consistent and not contradictory when we looked at in detail.

But in general, going back to the inhalation

studies versus the -- there's a few inhalation studies short term. They're not developmental or sort of more extensive kind of studies. But the short-term studies show us that the inhalation exposure comes up with a lower LOEL than the oral exposures. So from a pharmacokinetic situation -- see, endosulfan is basically primarily excreted by biliary excretion. So you're looking in the feces and you're seeing -- it looks like a lot is absorbed, 85, 80 percent. But the question is: Does it really go systemically? And we don't really know the answer. But it appears to us that it's going out through biliary excretion and that's why inhalation exposure's a little bit more sensitive than oral exposure.

Almost all of our basis for the NOELs are oral studies. So we have some concern that maybe inhalation studies, if we had them, would have a lower LOEL. So that's one reason we're suggesting an additional --

CHAIRPERSON FROINES: I think that you could -- from a pharmacokinetic standpoint you can argue that the inhalation is going to produce more chemical into the central nervous system right away than an IP study. And so your brain dose is going to be higher, I think.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Well, the IP studies are okay because the IPs don't have the first pass effect. It's the oral studies, the dietary studies.

So that's kind of like one issue. The other issue is, there happened in particularly some of these, let's see, you called them university studies or whatever they were, they did show male reproductive effects. And that was of concern to us, and that's an uncertainty for us. We don't feel that the subsequent studies, even the most recent study, 2006, negates our concern for the earlier studies, because of the way -- the study design, just kind of in general.

And Dr. Vidair has some slides he can show.

CHAIRPERSON FROINES: Could we go on to the next slide.

DPR STAFF TOXICOLOGIST SILVA: Yes.

CHAIRPERSON FROINES: George, are you talking about the studies at the top of this? Are these the studies that you're talking about?

DR. VIDAIR: Yeah. My name is Charles Vidair. I'm from OEHHA.

Yeah, some of the studies that I'm going to talk about -- I have three, four slides that I think --

CHAIRPERSON FROINES: Yeah, please. Okay.

DR. VIDAIR: -- show what we want to say pretty briefly.

CHAIRPERSON FROINES: Go ahead.

DR. VIDAIR: How could I get this computer to

project on the screen?

CHAIRPERSON FROINES: Just plug -- where's the projector?

DR. VIDAIR: Dr. Froines, the question you just asked George about the inhalation being more sensitive. Well, the problem we see is that a lot of the -- all the developmental and repro studies were not done by inhalation. They were done by oral. So that may be why they're giving us higher NOELs and LOELs. And if they had been done by inhalation, which is what we're concerned with here, inhalation exposures, they may have been lower.

And let me show --

CHAIRPERSON FROINES: That's exactly what I was saying. And what I was saying is what you just said. I mean I -- the IP studies are -- I think if we looked at the pharmacokinetics of inhalation versus IP, we know all these arguments. We've been having them for years. And so my sense is that you're going to get a greater dose to the brain by inhalation and that's going to impact the outcome.

DR. VIDAIR: So here are our rationale for adding an uncertainty factor when calculating infant RfC's for endosulfan. So this is an uncertainty factor of 3, which we would use in addition to the interspecies of 10 and inter-human variability of 10. We would add an additional

3 for the infant risk calculations.

There are three reasons: Pharmacokinetic differences between oral and inhalation routes; number 2, inadequate testing of young developing animals; and, 3, increased sensitivity of young rats compared to adults.

--o0o--

DR. VIDAIR: The first one, the pharmacokinetic differences between oral and inhalation.

After oral dosing for endosulfan, we find that most excretions in the feces, there's low excretion in the urine, and high accumulation in the bile.

After oral dosing, there are rapid kinetics of endosulfan entering the liver and then going back into the GI tract, suggesting a strong first pass effect in the liver.

And, lastly, so the result we see is a significantly larger amount of endosulfan may reach the general circulation following inhalation compared to the oral route.

PANEL MEMBER BYUS: I've got a question.

Is there any enterohepatic cycling in this?

DR. VIDAIR: No, there's not.

PANEL MEMBER BYUS: So there is none. Okay.

CHAIRPERSON FROINES: I have a question that goes back to Joe and I arguing about DNA adducts and

genotoxicity.

You could think that a first pass effect if the ultimate toxicant -- if the ultimate toxicant is a metabolite, then the first pass effect could get you there faster than inhalation.

DR. VIDAIR: Well, it seems a lot of this then goes straight to the feces, into the -- back into the GI -- it's dumped back into the GI tract through the bile and then comes out in the feces. There's only -- in the two studies that I'm familiar with on the pharmacokinetics of endosulfan, only about 10 to 15 percent comes out in the urine. The rest is coming out in the feces.

CHAIRPERSON FROINES: That's a good point.

PANEL MEMBER BLANC: So let me see if I understand the difference in opinion between the Department of Pesticide Regulation and OEHHA.

Department of Pesticide Regulation is suggesting that based their review of the available data for effects on young test animals that there's no differential sensitivity for the outcomes that you looked at.

Whereas, OEHHA is suggesting that because of lack of inhalational studies, of effects on animals that are in utero or young or effects on reproductive -- prenatal reproductive effects -- pre-conceptual reproductive effects, that a correction factor of 3 would be advisable

for those high risk groups.

Is that correct? Is that the difference of opinion over the factor of 3?

DR. VIDAIR: We have more reasons for proposing this factor of 3, but that's one of the differences.

PANEL MEMBER BLANC: Yeah. But anyway, that's what it come down to; is that correct? Did I understand the difference of opinion?

CHAIRPERSON FROINES: Well, do you have more slides?

DR. VIDAIR: We have more slides.

PANEL MEMBER HAMMOND: Wait, wait. Actually Paul's point's important. I'm want to make sure I understand it.

I thought the -- I may have misunderstood, because you said something different than what -- I thought you said the 3 came from young animals versus adult as opposed to pre-birth in utero. Isn't it young animals compared to adults is where the 3 comes from?

DR. VIDAIR: I would say developing animals versus adults, yes. That's going to be last graph -- the last table I'm going to show.

PANEL MEMBER HAMMOND: Okay. But that is something different than what Paul -- I guess I'm trying to figure whether my understanding or Paul's -- which of

us understands you or --

DR. VIDAIR: Well, there --

PANEL MEMBER HAMMOND: Go ahead. Okay, go ahead and we'll go look at it.

--o0o--

DR. VIDAIR: So then I mentioned inadequate testing of young animals. The rat reproductive study from 1984, that's, you know, Marilyn mentioned, very important study, because this is multi-generational dosing of the animals. But in 1984 it didn't include a lot of endpoints that are required in today's guidelines, like sperm numbers and some developmental landmarks like preputial separation, some skeletal stains. And there are things that weren't measured back then that are required in the guidelines now. We see that as a problem which we would address with -- partially with that uncertainty factor.

And then in order to address those problems, there was this recent Gilmore study development, a neurotoxicity study which included gestational and lactational dosing of rat pups via the dam. But there was no direct dosing of the wean pups from ages three to six weeks. So we see this again as a shortcoming that we would address.

--o0o--

CHAIRPERSON FROINES: I'm sorry. What does it

mean when you say this is "a shortcoming we would address"?

PANEL MEMBER BLANC: Well, you would address with a factor of 3 --

DR. VIDAIR: Yeah.

DPR STAFF TOXICOLOGIST SILVA: Could I make a comment?

They didn't -- see, the three to six weeks and on would have been addressed in the repro study and then gone on.

CHAIRPERSON FROINES: Marilyn, put your mike up like this.

DPR STAFF TOXICOLOGIST SILVA: The weaned -- okay, the age three to six weeks and further would have been addressed in the repro study.

PANEL MEMBER HAMMOND: But that study did not include gestational dosing, did it?

DPR STAFF TOXICOLOGIST SILVA: Yes.

PANEL MEMBER HAMMOND: It did?

DPR STAFF TOXICOLOGIST SILVA: That included pre-mating, mating, gestation, lactation, pre-mating for two generations with two litters per generation.

DR. VIDAIR: That's true. But it had things that it didn't do that are required today, like sperm numbers and developmental landmarks. So we think the '84 study,

you know, has some things that they didn't as a problem. And they weren't -- and in the Gilmore study didn't negate -- didn't make up for all those problems

DPR STAFF TOXICOLOGIST SILVA: The Gilmore study did look at the -- the sperm effects we're pretty much the issue at 21 and 75 days. That's --

PANEL MEMBER BLANC: Well, let me finish the point then that I was moving towards with the issue of 3.

The data from the LOEL value of 1, which becomes then we decided a value -- a NOEL value of .1, as compared to our other operative LOEL value -- NOEL value of .194 is essentially a factor of 2 of greater sensitivity of the youngsters for the endpoint of weight loss, I guess it was.

DPR STAFF TOXICOLOGIST SILVA: Right.

PANEL MEMBER BLANC: Is that -- would you agree with that?

DPR STAFF TOXICOLOGIST SILVA: Right.

Can I also point out though in the Sinha in 2001, where they only used three dams per dose, they also did not treat the pups postnatally, and only observed them at postnatal day 100. But at postnatal day 100 they looked at those effects. And the other later studies they looked at postnatal day 140 and there was no effects.

PANEL MEMBER BLANC: Right, I understand you have

negative studies. But you have this positive study that would give you a value of .1 compared to .194, which is a correctional factor of 2.

CHAIRPERSON FROINES: It actually would not, because if you follow the OEHHA position as they stated it, the uncertainty factor that they're proposing would be 3. So that would be a number of .33.

PANEL MEMBER BLANC: All I'm -- the point I'm trying to make is that you already have evidence that it's not absurd to use a correctional factor of 3 based on your own data, at least in terms of this one study. So I'm a --

DPR STAFF TOXICOLOGIST SILVA: Based on which study?

PANEL MEMBER BLANC: The Sinha study.

CHAIRPERSON FROINES: So, Paul, can we go on and let OEHHA finish, and then we can --

DR. VIDAIR: Yeah, just one more slide.

--o0o--

DR. VIDAIR: So this is -- these are all studies discussed in the RCD TAC document. And there are three comparisons here where the variable was age, comparing pups to adults or young animals to the adults, to look for differences in sensitivity to the endosulfan.

So the first two studies, the Zaidi study and the

Seth study are IP dosing. And the last comparison there, the Sinha '97, are actually two different studies from the same group, the '97 and '95. That was gavage dosing.

So we just simply compared the LOELs for these effects. And these effects could be called developmental neurotoxic effects, like serotonin binding in the brain and fighting behavior.

And the last two -- the Sinha studies would be male repro effects to the sperm.

So the difference between the young animals and the adults in the first two IP studies is 3. The difference in the last comparison is 2. So this we use as a guide for what we would propose as an uncertainty factor for the increase sensitivity of the young to endosulfan.

And we think that, you know, the pharmacokinetic argument supports some type of uncertainty factor. And the testing inadequacies support some type of uncertainty factor. And this we just used as a guide in coming up with a number.

DPR STAFF TOXICOLOGIST SILVA: I wanted to point out that in that Seth study, as I said before, there was not necessarily a 1 to 3 because there was nothing below 3 tested in the adults. And that was the study where 0.5 was the NOEL for pups. And even with, as they were talking about, the first pass effect being 50 percent,

perhaps you would still have .25, so it's still a higher NOEL than the inhalation NOEL that we're selecting.

DR. VIDAIR: Well, we don't know what the first pass effect is, you know, in quantitative terms. It could be greater, it would be less than. We don't know it. I'm not sure why you say 50 percent. But that's really an -- we see that as an uncertainty in trying to understand how to apply these developmental studies to an inhalation exposure.

PANEL MEMBER BLANC: And can we have --

PANEL MEMBER BYUS: Yeah, I just might add on that one regarding -- I mean in classic drug studies when you have a drug that you give orally that exhibits a high first pass effect, this is an indication of marked variability across the population, including young people and old people and diets. And there's unbelievable number of things that can affect the first pass effect. And so it gives you a much greater, broader range of dose response effects among age and whatever. I mean it's classic, just that fact alone.

So I see no reason why it wouldn't apply here as well. If it exhibits a first pass effect, it's highly cleared by the liver, that gives you a much greater variability no matter -- any time you do any study, because you can't control for all the variables. So I

mean it makes sense.

And so to my mind, it adds to this argument of the additional 3, is what I'm saying anyway.

PANEL MEMBER BLANC: Can someone put for us in context just for comparative purposes the current EP -- federal EPA guidelines on the additional factor of 3 for childhood or reproductive effects? Do they have a policy approach?

DPR STAFF TOXICOLOGIST SILVA: There's is a case-by-case basis. They don't as far as I know have a policy.

DR. VIDAIR: Do you mean for endosulfan specifically?

PANEL MEMBER BLANC: No, I meant more generically.

CHAIRPERSON FROINES: Do you have a generic -- you do have a generic approach?

OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah. This is George Alexeeff. And, you know, in February we're going to be bringing hopefully our first children's document with reference levels, and it will spell out the numeric approach that we're using. So what we're proposing here -- or what we're saying is consistent with that, but it's a little bit early because you haven't seen the report yet.

So we do have an approach in mind and -- but in this case we're just looking at the data. And our sort of sense is that there still are some additional remaining uncertainties which are not accounted for in the traditional uncertainty factors used, and that's why we're proposing that we would use an additional uncertainty factor up to 3.

DPR STAFF TOXICOLOGIST SILVA: And our opinion Is that we are protecting for a neurotoxicity. And when we protect for neurotoxicity, we'll be also more than protecting for any kind of repro effects.

Can I just finish my slide here? I have --

CHAIRPERSON FROINES: Sure.

The Panel needs to think clearly about this debate and decide on what recommendation we want to make. As far as I'm concerned, we're talking about a chlorinated pesticide that's one of the old organic pesticides. It's been around for the dawn of time practically. And there are probably 20 countries in the world that have banned it, and for which there is no use whatsoever. And the United States is still debating regulation. And we are here today debating differences between .194 and 1 divided by 3 -- which is what?

PANEL MEMBER BLANC: Well, I think .194 divided by 3 is the point.

CHAIRPERSON FROINES: Yeah, .194 divided by 3. And so we're talking about a factor -- we are debating a factor of 3. Which the point I'm trying to make with my bad math is that we've got to be careful about angel -- the number of angels dancing on the head of a pin, you know. And so in my view the two -- my view would be that the two agencies should meet to try and resolve this, if at all possible, based on the recommendations that we make out of this meeting today.

PANEL MEMBER ATKINSON: Point one sounds good.

PANEL MEMBER BLANC: Well, Let's see your last slide.

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DPR STAFF TOXICOLOGIST SILVA: I think the most important thing here is that the highest endosulfan exposures for infants and children is diet. Endosulfan is rapidly metabolized and eliminated orally. In one to two days it's virtually complete and by seven days 90 percent in animal studies.

Subchronic inhalation -- the animals that were treated in the subchronic study were four to six weeks at initiation, which means they were very young, post-weaning, adolescent, young adult. And there were no effects on the male reproductive organs as far as gross or histopathology. And in subchronic studies they look at

the prostate as well as the testes and the epididymis. And there is no consistent or repeated evidence that young males, whether fetal, neonatal, perinatal, weanlings, are more sensitive to the effects in the reproductive tract or for reproduction than are adults.

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DPR STAFF TOXICOLOGIST SILVA: DPR is concerned about protecting the health of fetuses and young children. And the inhalation and oral NOELs selected are adequate to protect for the most sensitive endpoint, which is neurotoxicity, as well as for reproductive effects.

CHAIRPERSON FROINES: Thank you.

So what I would -- Tobi, what I would really like to avoid is a letter from this Panel in which in the letter we say there is a difference in protective levels between the two agencies, and the panel feels whatever they feel. In other words, I would really like to avoid sending a letter forward to Mary-Ann that gets into this little debate -- not little, but debate. And I don't think it serves anybody's interests, you know, to have that.

So I think we need to figure a way to make it go away if it's at all possible. And so that's my sort of policy view of it.

But, anyway, I'm prejudging. I don't -- I think

the Panel needs to discuss how they view what's been presented.

And, Joe, you're the lead, so --

PANEL MEMBER LANDOLPH: Well, I mean I think both sides presented reasonable arguments and they debated vigorously. I have my own personal opinion, and I've been struggling for a time to bring it up. And that was that very nice section on illnesses that was written. That's bothered me since the beginning of our discussion with this chemical. So as far as I'm personally concerned, because there were evidences of numbness and tingling and other sensations, which are basically neurotoxic, I'm delighted to grab for any excuse to make the standards more conservative to protect public health.

So that's how I feel about it.

CHAIRPERSON FROINES: Paul.

PANEL MEMBER BLANC: Are we still waiting for the presentation about the addition of the dietary intake source? Or was there something -- is there something else that's --

DPR STAFF TOXICOLOGIST SILVA: You were asking about that table that --

PANEL MEMBER BLANC: I was referring really to the OEHHA commentary.

Did I misread the OEHHA findings in which they

emphasized not simply this adjustment factor for the infants? But wasn't there an issue about total source exposure, or did I just completely misunderstand that?

Would someone help me out here.

OEHHA DEPUTY DIRECTOR ALEXEEFF: We don't have an issue on that.

DPR STAFF TOXICOLOGIST SILVA: There's something in a dietary where people --

PANEL MEMBER BLANC: Dietary --

DPR STAFF TOXICOLOGIST SILVA: -- 55 plus, that was -- I think that -- I just saw that table.

PANEL MEMBER FRIEDMAN: Can't hear.

PANEL MEMBER BLANC: It's this issue about the -- let me see if I can tell you the points though.

OEHHA DEPUTY DIRECTOR ALEXEEFF: This is George Alexeeff. Yeah, we didn't have a specific issue on the total exposure question. We didn't raise that in our findings.

PANEL MEMBER BLANC: Aggregate margins of exposure, aggregate.

DR. VIDAIR: Well, we just reported what we read in the RCD TAC. We don't have an issue with that.

PANEL MEMBER BLANC: Okay. So you don't disagree with their approach?

DR. VIDAIR: That's correct.

PANEL MEMBER BLANC: I read it differently. So I apologize.

So, therefore, the only outstanding difference of opinion between the two agencies is the factor of 3; is that correct?

DR. VIDAIR: Yes.

CHAIRPERSON FROINES: No.

(Laughter.)

CHAIRPERSON FROINES: We still need to resolve the genotoxicity data issue.

DR. VIDAIR: Right.

PANEL MEMBER BLANC: That is a difference of opinion between the two agencies as well, is that correct, how you would characterize --

DPR STAFF TOXICOLOGIST SILVA: Whatever, that's...

CHAIRPERSON FROINES: Because Joe and I -- Joe had one position this morning and I suggested a difference. So that we need to at least bring this genotoxicity to closure, because Joe said he thought it should be stated that the compound is genotoxic when he spoke about it a few minutes ago. But at another time he had agreed to the OEHHA language that I suggested a small change. So you said two --

PANEL MEMBER LANDOLPH: Let me say what I said

rather than what you think I said --

(Laughter.)

PANEL MEMBER LANDOLPH: -- because I have been consistent all along, that I think that this material is genotoxic. And I pointed out in great detail my reasoning why at the first meeting.

CHAIRPERSON FROINES: I understand all that.

PANEL MEMBER LANDOLPH: And I reiterated my findings here. And I said I liked the OEHHA wording with your suggestion that we just take out the word "some". It says that it has -- although it's negative in some studies, it has genotoxic effects, period. And I think that's a balanced assessment. I could live with that.

And so that's my position. And it's been a consistent position all the way through.

CHAIRPERSON FROINES: Good. Okay.

I didn't mean to say you were inconsistent. I just wanted to clarify the issue.

PANEL MEMBER BYUS: So I'd like to chime in on that too. I mean I know, Joe, you've been very consistent saying that from the beginning. I agreed with you the first time, I agree with you now. I agree with your statement in your written review, which I will read. That says, "The reviewer" -- meaning Joseph Landolph -- "is now convinced that endosulfan is a genotoxic agent that can

cause chromosome aberrations, micronuclei, mitotic gene conversion and reverse in yeast, inhibition of gap junctional communication, as also a tumor promoter." And I concur completely with those statements.

And I think it's not clear in the Executive Summary -- I mean I don't know whether it was going to be rewritten or not, but the statements that are in the Executive Summary dealing with genotoxicity are, in just partial quotes, "No evidence for oncogenicity was observed, and, "There was inconclusive findings from contradictory results of genotoxicity." I mean which does not say that at all. So I mean I really find that sort of a seriously deficient kind of statement.

And then back to the additional factor of 3. If you believe that this is genotoxic or moderately genotoxic or has genotoxicity, then you really don't need to know any more than that to apply an additional developmental child sensitivity or factor of 3 based on whatever NOEL you choose from whatever mechanism. And so that's how I would do it. I mean if it is genotoxic or if there's some strong evidence that it is or reasonable evidence, then that's all you really need to know.

And I think that -- but the additional factor is, as I said before, because of its extreme first pass effect, it's the likelihood of metabolism either

contributing to its genotoxicity or to its clearance. And, again, you don't know. And you also have the alter distribution of all the SIP enzymes -- P-450 enzymes among neonates versus children versus adults. But there's such a degree of uncertainty there, that I mean I think it'd be a remiss if you didn't apply the additional factor of 3.

PANEL MEMBER LANDOLPH: And could I amplify that. And it was a very nice statement you just made.

I've been concerned where we've had some MOEs of 1 or less than 1. I think it was the corn growers and the harvesters or the aerial sprayers. You know, they're neurotoxic symptoms. So in certain instances we're kind of on the edge with this compound. To paraphrase from Paul's comment earlier, an elephant in the room is if this is genotoxic, then we're not talking about thresholds and stuff like that. You know, in the future we could have bigger problems with this. So I would urge conservatism, because this chemical is a bad actor to begin with.

CHAIRPERSON FROINES: I strongly agree with you on your statement about metabolism. I think that the data in this document on metabolism -- it's not her fault -- but the literature on metabolism is so inadequate that you can't make head or tails. I mean this compound's very complex and is going to have multiple pathways depending upon which enzymes. And so for all you know -- I'll say

it. For all you know, you know, it could lead to a quinone.

(Laughter.)

CHAIRPERSON FROINES: That's a joke, Paul.

(Laughter.)

CHAIRPERSON FROINES: But the point is, to be serious -- I'm not suggesting that because I don't actually think it could happen because of its structure -- but the metabolism is really very, very limited. And so I think that is an area of significant uncertainty.

Now, let me just say for your benefit, Craig, and everybody's benefit, what Joe and I decided this morning was that the document should contain the following sentence: "Thus, while several standard assays were negative, there is evidence that endosulfan is genotoxic." That's what we -- now, if you think -- that's a slightly modified OEHHA statement in which I took out the word "some". So if you want it to be a stronger statement the way you've articulated it, then that's the point of discussion.

PANEL MEMBER HAMMOND: What do we normally do given -- isn't there normally mixed genotoxic data? Isn't that -- isn't it pretty rare that --

CHAIRPERSON FROINES: It's always --

PANEL MEMBER HAMMOND: -- all genotoxic tests

would be positive?

CHAIRPERSON FROINES: Right.

PANEL MEMBER HAMMOND: It's almost always mixed, correct?

So is this a caveat that you're adding that you wouldn't add for anything else, that although some were negative? You wouldn't say that ordinarily, would you?

CHAIRPERSON FROINES: Well, that's a decision the Panel needs to recommend.

PANEL MEMBER HAMMOND: Oh, let me -- I'm just asking in a standard compound, 3,4,5-trimethyl chicken wire, and you have mixed results, would you say, "although some were negative"?

CHAIRPERSON FROINES: But, see, I want to keep emphasizing the same point. The old EPA 100 in vitro tests were bad, because when they did studies at NIHS and NTP, they found that a lot of the tests were measuring the same basic endpoints. And so they weren't really -- you could take two tests and get the same results and you hadn't learned anything. In other words it didn't reinforce the outcome.

PANEL MEMBER HAMMOND: That's right. That's not what I'm saying.

CHAIRPERSON FROINES: But what I'm saying is -- what I'm saying here is the -- yes, you can have

negative results. But when you look at it from a mechanistic standpoint, the fact that you have DNA adducts and environmental health perspective studies that are much more modern than the old '70s tests, then you have to say that there is evidence for genotoxicity.

PANEL MEMBER BLANC: John, I think that part of the discussion maybe is going off track a little bit because we're mixing up different things. The question isn't: What is the wording of the OEHHA commentary on the DPR document? The question is: What will the ultimate DPR document that comes to the Panel for our findings say or not say? And I think that's the fundamental issue. So when I think about that, the question from me is: Are there points here which could be generalized? And were they to be generalized, would they be generalized in a direction I would be supportive of or not supportive of?

So for me, for example, the application of the threefold factor adjustment, even though this will always have to be done on a case-by-case basis: Am I anxious or not anxious about a decision that could have implications or precedent setting in terms of the Panel's general approach and in terms of the Panel's consistency in approach of dealing with chemicals whether they're brought to us by OEHHA or they're brought to us by the Department of Pesticide Regulation?

And it's always been the approach of the Panel in my experience to be public health protective in its thrust. And, therefore, in situations where data are insufficient or not convincing, that one errs on the side of taking that uncertainty into account.

Therefore, I think on the whole, the OEHHA input is more convincing to me than the very difficult position of having to argue the negative from imperfect data, which is not the fault of the DPR, but the data has its limitations.

DPR STAFF TOXICOLOGIST SILVA: But there's so much more positive. I mean there's so much more data that show that there isn't.

PANEL MEMBER BLANC: Well, I think that Craig's point -- if you want to be consistent with our policy in terms of childhood and infancy is that in our general policy guidelines we actually have been approaching genotoxicity -- evidence of genotoxicity as being another factor that weighs on our decision in terms of being protective for infants and children.

I fully agree with John that we also don't want to be setting a precedent of getting in the midst of an argument between OEHHA and the Department of Pesticide Regulation. I would prefer that the final document come to us worked out in advance.

I would say also that in terms of precedent, I certainly am not willing to conclude a finding at this meeting of the document, which came to us through no one's specific fault in an incomplete form -- I want to point out for the record that it not only was missing those first three pages. But if you look, it is missing pages 193 through 196, the concluding four or five pages, in which many things were summarized.

So I don't think that, even if we didn't have these other problems, we would be able to have a tentative adoption of findings today.

But I would echo John's comments and urge very strongly that DPR recaucus with OEHHA and try to work this out. Otherwise it may lead to an even more unfortunate precedent.

CHAIRPERSON FROINES: So we've heard from Craig and Kathy.

But I don't know if you were finished or not.

PANEL MEMBER HAMMOND: That's right.

CHAIRPERSON FROINES: You're finished?

PANEL MEMBER HAMMOND: Do you mean on this exact issue or about -- the genotoxicity or do you mean overall?

CHAIRPERSON FROINES: Well, the discussion we've been having right now is -- we were talking about the threefold safety factor. But --

PANEL MEMBER HAMMOND: Well, I guess --

CHAIRPERSON FROINES: But then genotoxicity is rearing its ugly head behind --

PANEL MEMBER HAMMOND: Yeah, when you asked me that, I was finished.

If we're just talking about this whole picture, I think that it is very important to resolve the genotoxicity issue. I agree that we don't just count the number of studies that are done and wherever the majority rules. It's not that kind of thing with genotoxicity. And one has to look at the data carefully and understand the complexity of genotoxicity data. And having a few positive endpoints is disturbing and needs to be noted and seen in that manner.

In a similar way, I think the question of the increased uncertainty I find rather compelling. And I think -- but I do think it's most important that the two agencies work that out. That would be ideal from the State of California's point of view and the public protection. So I would like to see that done.

CHAIRPERSON FROINES: Roger.

PANEL MEMBER ATKINSON: I have nothing to add. But I certainly concur with statements made by Paul, Joe, Craig, and you.

CHAIRPERSON FROINES: Charlie.

PANEL MEMBER PLOPPER: I don't really have much data. I think that the preponderance of evidence for most scientific studies is that fetuses and young children are going to be more sensitive, more susceptible than adults and that it really -- these days I think the evidence has to be the other direction, that a strong proof that this is not the case. And I think that Table 7 in OEHHA's document pretty much makes a strong enough argument to suggest that if you have to have the doubt, then it's really a factor of 3 seems to be a strong doubt.

But I would also be strongly in favor of having the two agencies work this issue out and come up with some kind of an agreed statement, because it seems silly to have to make this argument again on every one of these compounds when there's still -- so far there's no real evidence when it's looked at hard that there's -- there should be any reason not to assume that this is the case.

CHAIRPERSON FROINES: Thank you.

Gary, you're --

PANEL MEMBER FRIEDMAN: I'm still not as alarmed as everyone else is. So maybe I'm wrong about the possibility that the two agencies disagree. I mean there's often disagreement in scientific conclusions, especially with incomplete evidence like they have. So if they -- I think they should try to come to an agreement.

But if they can't, I think we can deal with that by saying, you know, the difference is still -- both agree that it's a toxic air contaminant, and we tend to prefer the health conservative approach with the additional uncertainty.

I would like to have people tell me why it's so important that they agree. I think I'm missing that.

CHAIRPERSON FROINES: Well, I think that it's -- the issue isn't one of disagreement between agencies. That's the outcome. But I think that the -- there have been issues raised about the genotoxicity as a factor of uncertainty. The metabolism was a factor of uncertainty. The inhalation versus IP is a factor of uncertainty. And geno -- what'd I say? -- genotoxicity, metabolism, IP versus inhalation, other pharmacokinetic issues. And I'm -- and a couple of the studies that were shown.

So it seems to me that there is this general question that I think Charlie said perfectly, which is: Do we have -- do we have not a belief but at least a sense that there is the potential for children -- I mean non-adults having greater susceptibility? And I think what's been said here is that there is a generic belief that that is possibly true.

And so given all those factors and given that we want to be consistent, we would think that the outcome is

in fact that the threefold safety factor should be incorporated. And so that's the position we're taking. We're saying it would be better in the -- for sending off to the Director if we could get agreement. But the point is still the science, not the policy, in a sense.

PANEL MEMBER FRIEDMAN: I guess I misunderstood. So I thought there was something about policy, you know, that --

CHAIRPERSON FROINES: No.

PANEL MEMBER FRIEDMAN: So that we're really telling DPR that we think they should adopt the more conservative health concerns?

CHAIRPERSON FROINES: Right. That's what everybody has -- everybody who's spoken has said it. It's unanimous.

PANEL MEMBER FRIEDMAN: Okay. So it isn't the issue of the disagreement, but that --

CHAIRPERSON FROINES: No. That's just -- I'm trying to avoid putting your dirty laundry out in the public.

PANEL MEMBER FRIEDMAN: Okay. I totally agree with that.

PANEL MEMBER PLOPPER: You know, I think it's going to help when this document that George was talking about comes out, so that there can be discussion --

PANEL MEMBER FRIEDMAN: Could you speak into the microphone, please.

PANEL MEMBER PLOPPER: Pardon?

PANEL MEMBER FRIEDMAN: Closer to the microphone.

PANEL MEMBER PLOPPER: Oh, sorry.

I think it will help when this document that George was talking about comes out, so that it would look at all of what the scientific basis would be of evaluating whether for a particular compound infants or young children are more susceptible than adults. And I think that's going to help.

CHAIRPERSON FROINES: Do you have more to present this morning?

No.

Well, thank you very much, Marilyn.

So as of -- at this point I think we have finished endosulfan for this session. Tobi and I had hoped to go further with it today, but we're obviously not going to do that.

So what we would like to do is at the next session we'll have hopefully a final session on endosulfan and we'll have findings at that meeting. So we'll have -- and this will be February 28th. And we're going to be presenting -- we're having a joint meeting with the Air Resources Board. So we'll all have to be on our best

behavior.

(Laughter.)

PANEL MEMBER FRIEDMAN: I'd like your reaction to something I've offered to do. That mass of findings I think just had too much, the draft that we got. By the way, there was only the first 12 pages that didn't seem to have an ending. But how would you feel about my attempt to shorten it to something much briefer?

CHAIRPERSON FROINES: I haven't seen any findings.

PANEL MEMBER BLANC: No, the info -- excuse me. Those were OEHHA's findings, not our findings. Those were not our draft findings.

PANEL MEMBER FRIEDMAN: Oh, I'm sorry. I thought that was our findings.

CHAIRPERSON FROINES: Kathy and Joe would normally be working on the findings and I would do the final edit. And --

PANEL MEMBER FRIEDMAN: Well, anyway, I --

CHAIRPERSON FROINES: But how about if you and -- if Kathy and Joe did a draft and then you did an edit? That'd be great.

PANEL MEMBER FRIEDMAN: I'd be happy to do that.

But I was reacting incorrectly to what I received, thinking that that was our findings. And

obviously it was not.

CHAIRPERSON FROINES: No. We have no findings yet. And obviously there are issues that are going to influence what's in the findings. Although we've actually got -- we have unanimous view of this document, as far as I can tell. So that we cannot write our findings now.

PANEL MEMBER FRIEDMAN: Okay. I may not have a problem at all with what, you know, the draft says. But I'd be happy to look at it.

CHAIRPERSON FROINES: So I think we should work on the findings just so we can put this one to bed. We're arguing about big issues but very small changes in language, I think.

Yeah, Joe.

PANEL MEMBER LANDOLPH: And we'll have a new copy of the final document as DPR has finalized it before the February meeting?

CHAIRPERSON FROINES: Yes.

PANEL MEMBER LANDOLPH: Could I request --

CHAIRPERSON FROINES: I hope so.

Tobi, Joe just asked if we'll have a final draft from you to read before the February meeting.

DPR ASSISTANT DIRECTOR JONES: That's correct.

PANEL MEMBER LANDOLPH: Could I make a request.

Is it possible to get a very nice copy of the

document like Marilyn gave me by e-mail but in hard copy, with the document with the very nice yellow so it's easy to see the changes?

CHAIRPERSON FROINES: Well, if you can do the yellow, that would be great.

You're going to get a hard copy anyway and an e-mail copy, I think. And so --

PANEL MEMBER LANDOLPH: I just don't want to burn out too --

CHAIRPERSON FROINES: It's just that if you -- I don't know. Is it easy to get somebody to highlight?

DPR ASSISTANT DIRECTOR JONES: We'll do it.

CHAIRPERSON FROINES: Yeah, this is a big document. So that it would really be -- that would be highly beneficial.

PANEL MEMBER LANDOLPH: So that we agree that Kathy and I will start findings between us and go back and forth and then distribute it to you and the Panel to look at? Is that how you would like it done?

CHAIRPERSON FROINES: Yeah, I think -- I should just say that I think the discussion by the Panel today has been extremely good. Everybody was well prepared and everybody was extremely articulate in their views. And so I think this transcript will read very well in terms of the Panel's review of this document.

And, see, Bill Lockett just gave me a thumbs up. He loves this meeting today because he loves the discussion of the science. And so -- sorry, Paul.

PANEL MEMBER BLANC: You know, John, one other comment I would just make about something that may be a subtle misunderstanding or gap in world views between the DPR and OEHHA. And, that is, what constitutes the endpoints of greater sensitivity or susceptibility of younger members of the species? And although neurotoxicity and reproductive toxicity are two key examples of what might be endpoints of increased susceptibility, in fact any evidence of an endpoint which was manifest more strongly in the young would be evidence of greater susceptibility of the young. And perhaps that is a source of some confusion or difference of opinion that could come together.

So that, you know, even were there to be convincing evidence that there was no greater degree of neurotoxicity in the young, let's say you had the inhalation studies which showed no difference in NOEL, but you had studies which showed other effects, respiratory or systemic, nonspecific, in the young that were greater, that would be evidence for greater susceptibility. It doesn't have to be reproductive or neurotoxicity from the point of view of why from a policy point of view one would

want to take such susceptibility into account. And I think that's an important point that DPR should put in context.

CHAIRPERSON FROINES: Well, I think -- I think these are the kinds of issues that OEHHA is thinking about in the document that they're going to bring us in February. Is that right, Melanie?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Yes.

CHAIRPERSON FROINES: So that I think we're going to actually have a discussion on the Panel on this particular issue as we review that.

And I would add one more thing which I think is important. And, that is, that DPR in its approach to toxic air contaminants uses the weight of evidence. And I think that that's fine, but I think one has to establish criteria when you have mixed results for how you're going -- what is it going to take to find something positive rather than negative. Because if you do have mixed results, obviously there's some uncertainty. And it seems to me that there needs to be -- and I hope you guys talk about this -- there needs to be some criteria established. I mean one of the papers I read on genotoxicity was extremely sophisticated advanced science. And so I think we have to be thinking about the analysis

of the studies where we really look at, are these studies that are positive, are they really modern studies versus old studies that are less adequate? And so the criteria for weighting where you have mixed results is really pretty important.

I just want to say one other thing. Everybody who's in this field at least with the age that I'm reaching knows about the terrible studies that NCI did by contract in the seventies. I mean there's a whole history of the failure of NCI to conduct effective studies. And so when we get around to looking at studies from that period of time, it may not be surprising that they turn out to be less than adequate.

Do you agree with that, Melanie?

You weren't giving me the --

PANEL MEMBER BYUS: She wasn't born then.

CHAIRPERSON FROINES: She wasn't giving me the facial response that I wanted.

(Laughter.)

CHAIRPERSON FROINES: I'll ask Andy.

No, no, let it go.

But, anyway, there were significant problems with NCI studies in the seventies. And we don't know if this one was part of that. But there was certainly horrible science that went on in some of those studies. So we'll

leave it at that.

Shall we take lunch?

PANEL MEMBER BLANC: Peter, can we leave material in the room, bags and things?

MR. MATHEWS: Yes.

CHAIRPERSON FROINES: I would like to start on -- we have a different schedule --

PANEL LIAISON BEHRMANN: One o'clock.

CHAIRPERSON FROINES: All right. We have a different schedule. I would like to start -- instead of with the three agencies at 1 o'clock, I'd like to start with our guest speaker so he's not -- and he's welcome to stay afterwards. But at least we'd give him the option to say his piece and then decide if he wants to hang out.

So if that's okay, we'll start with you at one o'clock.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

CHAIRPERSON FROINES: Peter, we're going to start.

MR. MATHEWS: We're missing two.

CHAIRPERSON FROINES: That's all right. We said 1 o'clock and we're at least 1:10. As soon as Landolph sits down, we'll start. And we'll turn it over to Melanie.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Good morning. Melanie Marty from Office of Environmental Health Hazard Assessment. Good morning -- good afternoon.

When I spoke with John about the symposium this afternoon, we talked about ways to get people to come up and talk about a specific methodology called quantitative structure activity relationships. And I just wanted to say why we're talking about this.

I think the Panel has said many times in the past that figuring out what chemicals to focus on is not a simple task. There's lots of different programs in California and in the U.S. and worldwide that have to look at laundry lists of chemicals and flag the ones that might be bad actors. So OEHHA's been looking around at other programs and other organizations that have to do this for one reason or another. And we've come to realize that

both U.S. EPA and FDA look at lists of chemicals where there either is no toxicology data known or the chemical's under development so there hasn't been a lot of study. And they use quantitative structure activity relationships to help them decide whether there's a potential problem with that chemical from a toxicological perspective.

So Ed Matthews is with us today. Ed's a computational toxicologist at FDA Center for Drug Evaluation and Research in their Informatics and Computational Safety Group. And Ed has developed either all or almost all of the QSAR models that FDA uses when they look at new drugs. So I asked him to come just to give us all an idea of what you can do with QSAR and how the models are developed. And that's why Ed is here today.

CHAIRPERSON FROINES: So just to -- I didn't give any introductory remarks. But this is a workshop on setting priorities for the Toxic Air Contaminant Identification Program.

And at some point I want to have a discussion, not perhaps in this workshop, but on the fact that we know that there are 180, approximately, hazardous air pollutants which don't have risk assessments for the most part. And one question is: Should OEHHA develop risk assessments for the HAPS from a standpoint of going

further on a regulatory basis? So that's an issue for the future.

There's an important issue, which is: We want to find things as toxic air contaminants and then we presume that ARB will -- presume will follow up with regulatory activity, as well as DPR. So that's an assumption and it's not always been the case. So that there are other issues that are worth talking about over time.

So welcome. And it's all yours.

(Thereupon an overhead presentation was Presented as follows.)

DR. MATTHEWS: Thank you very much. And -- let's see, is this microphone on?

PANEL MEMBER BLANC: Yes, it is.

DR. MATTHEWS: Okay. Great.

First of all, I'd like to thank John and Jim and Peter and Melanie and Linda and all the people that are involved in inviting me here.

It's a pleasure to be before this group. I spoke here a couple months ago. And this is going to be largely the same talk. So I'm afraid that if -- you know, if you heard the first one, you're not going to hear too much different.

My name is Ed Matthews and I work for the U.S. Food and Drug Administration in a very small applied

research laboratory.

All right. Let me figure out this computer. Where's the page down?

Oh, terrific.

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DR. MATTHEWS: As I said, it's a small group. In my last talk our Director, Joe Contrera, was on this slide, but he has since retired. Dan has been promoted to an acting director. He's our database manager.

We have a single chemist. We're in the process of hiring a pharmacologist.

And we have one student working with us, Anna Frid. She is actually a graduate of UC Berkeley. And she's helping me develop QSARs for cardiotoxicity, using human data. A terrific student. We have an excellent working relationship with UC Berkeley.

And Barbara Minnier helps us out with the QC in our data and our databases.

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DR. MATTHEWS: Okay. I'm going to try to cover four areas in my talk:

FDA decision support tools. I'm going to describe what they are.

A strategy for predicting carcinogenicity. We actually predict a lot of other endpoints. But I'm going

to emphasize this and the way we think about this process.

Give you some information on some of the preclinical clinical QSARs we have, which are basically your animal toxicology tests, like what you were talking about this morning for endosulfan.

And then QSARs based upon human data. This is data that comes back to us in terms of post-market surveillance for pharmaceuticals or information from clinical trials in patients.

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DR. MATTHEWS: Okay. So let's talk about the specific FDA decision support tools. And basically what we use them for is a matter of prioritizing large numbers of chemicals and try to get rapid and reliable decision support information right at the beginning of the process. And we're building a dossier on specific chemicals.

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DR. MATTHEWS: Okay. Before I get into that I want to give you, first of all, an outline of the mission of our group.

As I said, we're an applied regulatory research unit. That's actually our mandate, to create toxicology and clinical databases. And, in fact, that's where we started. We got support through our center director to do that one before we got into doing QSARs.

In order to do QSARs, however, you've got to translate that toxicologic data into some sort of a mathematical relationship that you can use for predictive purposes. So we spent a great deal of time developing rules for quantifying toxicologic and clinical data.

We also are in the business of evaluating predictive data mining and QSAR software. We've looked at most of the products that are available worldwide and have selected a subset of those for our use and purposes.

And the other thing we do is that we have these cooperative research and development agreements with a variety of software companies. And we use this as a matter of leveraging the particular research that we're doing as well as tremendously expanding the brainpower that we can put into specific problems we have to solve.

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DR. MATTHEWS: I'm going to start this talk by -- for those that aren't familiar, there's actually two types of QSARs.

There's what they call local QSARs. This is probably -- if anybody were familiar with the field, this is the type you're familiar with. It's a QSAR equation that's based on small sets of structurally similar chemicals. And this whole field was set in motion by Corwin Hansch at Pomona College out here in California.

In fact, he's still publishing. He's in his nineties.

These QSAR equations are able to predict activities of chemicals if they have a similar structure. And they usually involve just one or two very simple chemical molecular descriptors.

In contrast, there's what is known as global QSARs. And this is primarily what we've ended up working with and simply because the chemicals that we deal with are very dissimilar in their structures. They're like pesticides. You may get a couple of them that are fairly similar, but for the most part you've got large numbers of dissimilar molecular structures.

So with global QSARs you're able to use multifactorial, nonlinear QSAR equations to make your predictions.

And, in fact, these QSARs are able to induce very large numbers of molecular fragments or descriptors as the basis of these predictions.

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DR. MATTHEWS: In terms of the decision support tools, there's another way to look at it. You can describe them in terms of the types of information that you're trying to predict. And what we call the high end, so to speak, or the human/mammalian health effects, in this particular category you have this decision support

toolbox that actually is a collection of different QSAR programs that we have through our collaborators and expert systems.

The aim of these particular tools is to predict carcinogenicity or gene tox or reproductive and developmental toxicity, those sorts of endpoints, as well as being able to predict some very specific effects of molecules in humans using human data; in other words, very specific adverse effects to human organs.

In contrast, there are QSARs which you can use to predict environmental and non-mammalian effects of chemicals. And for those that aren't familiar, the U.S. EPA has been in the business a lot longer than we have, and they have a huge suite of local QSARs which enable you to predict environmental fate and aquatic toxicity and a variety of other endpoints.

More recently, the OECD has passed legislation. And, once again, I don't know if this group is familiar with it or not. But it's now actually been implemented. There's both a 7th Amendment, which deals with cosmetic products, and then there's the REACH initiative, which is involving a reevaluation of all the chemicals in commerce in Europe.

And under the REACH initiative they're essentially going to try to do this using QSARs and not

rely upon the results of animal studies, because they have to accomplish this in a very short period of time. There just isn't the resources or the money to do it otherwise.

And as I said, these types of QSARs are very, very good at predicting environmental fate and those sorts of endpoints.

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DR. MATTHEWS: Now, there's some unique features to the FDA system which I think you'll be interested and will appreciate.

First of all, because we use proprietary data in our models, we have to generate the QSARs in-house. So I mean all of the QSAR prediction paradigms and the QSAR models are actually developed by our staff.

Models contain knowledge from proprietary studies in a form that can be shared. Now, what I mean by that is that you can't actually put into your QSAR program, you know, the name of a proprietary substance or its complete structure or something like that. But what you can do is you can use the QSAR program to find parts of that molecule that are associated with some type of toxicity like carcinogenicity. And then that becomes part of that statistical information that's in the memory of the program, and it will allow you to share that knowledge. And this has been very important because of course we're

using a lot of proprietary substances from pharmaceutical industry and they're using our software products right now for that very purpose.

In addition to which, we've got some very specific requirements which I'm going to get into in a moment. But we actually go through and optimize and improve our programs and work with our collaborators to meet our own specifications. So we're very much involved in the whole process.

The other thing that's unique about our system is that the same training data set is used in more than one prediction paradigm. In contrast -- you know, historically people that have maybe purchased a site license for TOP CAT or one of the other systems, then they jump over to another program, and they expect the predictions to be somewhat similar. But unfortunately that's never going to be the case because they always use different assumptions, different training data sets, different methodologies, as well as different prediction paradigms.

Well, that's not the case here. We're actually using the exact same training data sets and they all go through the same annual upgrade in terms of the system.

Okay. Now, we do get a small CRADA contribution, royalty, whatever you want to call it, back from our

collaborators. And all of this money actually gets reinvested in the program. We're able to support students and contractors that help us extract data from our archives and et cetera.

Yes.

PANEL MEMBER HAMMOND: What's CRADA?

DR. MATTHEWS: I'm sorry?

PANEL MEMBER HAMMOND: CRADA, what is it?

DR. MATTHEWS: Oh, CRADA - Cooperative Research and Development Agreement. Sorry.

The government's full of acronyms.

(Laughter.)

DR. MATTHEWS: And as I said, also by having -- involving these other small software companies, it tremendously expands our expertise in terms of knowledge of the specific problems we're trying to solve.

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DR. MATTHEWS: Now, specifically, these are the programs that we're going to use. And in a moment I'll show you where you can get more information about it.

We've been using the MultiCASE software programs now for about eight years.

The META program you can use to predict metabolites. So I was thinking here when you were talking about endosulfan this morning, I mean it would be very

easy to put that molecule in there, and you could predict all possible mammalian metabolites of that particular pesticide.

The MC4PC is basically a toolbox which we superimpose our training data sets on that we've developed for all of our endpoints.

And this -- both of these programs make predictions based upon molecular fragments. So what they're basically doing is identifying certain pieces of molecules that are statistically and significantly enhanced in your training data set. For example, something like an alkylating fragment would be picked up in a mutagenicity module.

The second -- MultiCASE is located in Cleveland, Ohio.

Leadscope is a small company that's on the Ohio State campus. And they actually -- their primary business was in developing data mining software. But they got interested in predictive data mining about two or three years ago. And their program works very, very well.

So we're actually able to use two different programs to attempt to identify structural alerts associated with toxicity as well as making predictions.

There's also programs that make their predictions purely and simply based upon whole molecular descriptors.

What I mean by that, if you're not familiar with it, descriptors such as E-state, Log P, volume shape descriptors, et cetera, et cetera.

The one program, MDL-QSAR, we've had about five years of experience with. And just about every year there's a different company.

It started actually with SciVision. It's developed by Joe Votano. It was purchased by MDL. And MDL was purchased by Elsevier. And now it's back in California. Symyx is a California company. So it's quite a history.

The other program is BioEpisteme, which is developed by Prous Science. And they're actually a publishing company in Barcelona, Spain. But they have a small research group. And we've been working with their particular software.

In terms of expert systems, DEREK for Windows you might be familiar with. It's been around for almost 20 years now. And they have also a program called Meteor, which allows you to predict the metabolites of organic molecules.

And interesting enough, if you happen to have both of these side licenses, you could actually compare the rules that were built into the program and the types of metabolites that you would get.

DEREK for Windows is a program that's licensed through Lhasa, Limited. That's a nonprofit institution in the UK and they're located on the University of Leeds campus.

The oncologic program was originally developed by LogiChem, and now is exclusively distributed by the U.S. EPA. That program only predicts carcinogenicity. But it's unique in the sense that it will do it for everything -- you know, everything from polymers and heavy metals and all sorts of, you know, very unusual substances which you're liable to run into as an EPA scientist.

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DR. MATTHEWS: Okay. In terms of getting some additional publications, I've had a number of them with regards to MultiCASE. Gilles Klopman is the gentleman at Case Western Reserve who developed the MultiCASE program.

Chihae Yang is a lead scientist who's published extensively with LeadScope.

Joe Contrera and our group published a number of papers with MDL-QSAR. I've come out with several with BioEpisteme

And then in terms of these other two programs, the lead scientists there are Carol Marchant. She's the one that heads up the knowledge group, as they call it, that develops the human expert rules for predicting the

mechanism of action of chemicals, which you can do with DEREK for Windows. And Yin-Tak Woo at the EPA is the lead scientist for the oncologic program.

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DR. MATTHEWS: Okay. Now, when you talk about -- you know, a lot of people use QSAR programs and they don't think too much about it. They just put a chemical in and push the button and, you know, they get a result and then they put it in a report. But we've taken it in an entirely different direction. We think it's really, really important that you do your homework and, in particular, that you statistically validate in an appropriate way your QSAR models; you know exactly what the model is doing and whether it's reliable or not. And there's a variety of ways you can do this.

Now, the leave-many-out process, which we use all the time, establishes the model reliability. And basically what you do is you take 10 percent of your training data set. This is the one we're talking about right here. Take it out of the training data set and then predict the activity of those 10 percent compounds of what's left over in the training data set. Then you repeat the experiment many, many times and it gives you an idea of how reliable your model is going to be.

And in a moment I'll show you how reliable our

models were for carcinogenicity.

The other test you can do is a leave-one-out, which tests the model stability. And you essentially leave one chemical out and then you predict its activity with the rest of the data set.

Okay. In addition to which you always want to run an external validation. You know, we build our QSAR models using every bit of data we can get our hands on. But then, you know, you come along and there's another 100 new chemicals that we get carcinogenicity studies for, et cetera. And these are novel, unique molecular entities. Different structures. And it's very important to use these types of chemicals to go back and just see how well your models work. I mean it's a very rigorous test for how well your QSAR model is performing.

In addition to which, we test for complementarity, which is kind of unique. Because as you'll see in a moment, we don't use just one QSAR program. We actually use several simultaneously. And there's really no point in the world using two QSAR programs to predict exactly the same things. I mean, you know, it's just a duplication of effort.

So the first thing we do is we make sure that the programs are predicting something different about the test molecules and there's something different about the

prediction paradigms, so we test for complementarity to make sure they are different.

In terms of the performance criteria, we focus in on specificity and false positives. And we try to make sure that the QSARs are performing well and have very few false positives and high specificity.

We of course need high coverage and high applicability domain. I mean if we get assignments in from our scientists and we routinely were to tell them, "Well, we can't make a prediction because your molecule isn't covered," they're not going to be very happy with us. So we invest a great deal of time in building large training data sets and have good coverage, I mean something like 95 percent of basically everything that we predict.

As I said, multiple QSAR programs with identical training data sets.

And the other thing is we use a standard weight of evidence scoring paradigm. And I have to admit when I was thinking about your endosulfan discussion this morning, I mean this is at the heart of what we do. We often times have more than one study for a particular endpoint, we have more than one source of information. The relative activity of chemicals in the same test are often times dramatically different. So we have a

standardized way in which we relate the relative potency of substance in these tests and give that a weight of evidence in the QSAR equation. And I'll have the example of that in just a minute.

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DR. MATTHEWS: Okay. Now, in terms of using more than one program, as I said, we do use two or more programs. There's two ways you can use them. You can use -- you can get a high confidence prediction and specificity by only taking consensus positive predictions. So in other words, you're getting the same prediction from two or more programs that are complementary. They're both predicting the substance to be positive. And yet one's doing it on the basis of descriptors, another's doing it on the basis of molecular fragments. To us that's really convincing information.

The other way you could do it though if you're, you know, prioritizing large numbers of chemicals and you're worried about sensitivity in trying to capture all possible positives, then you could do it this way essentially: You know, take all of the validated programs. And whatever you get a positive, you can add that together. But you will sacrifice specificity by going that route.

Now, the other important thing that -- and

frankly we haven't started to do this until the last year or so. But we think it's really, really important to combine the QSAR predictions with some sort of a plausible explanation of why the chemical caused that toxicity.

So, as I said, we have two programs that give you structural alerts that you can compare with what's in the literature and what people know.

The other thing, with your expert systems you can actually get a reasonable mode of action prediction from the DEREK for Windows program. And it gives you a long list of references and -- that is the basis for that plausible argument why the chemical had that particular action.

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DR. MATTHEWS: So let's talk about carcinogenicity in rodents.

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DR. MATTHEWS: The database we have has about 25,000 records. The information has been brought in from a number of sources:

Your NTP technical reports, which I know you're familiar with.

A lot of the studies have come in from pharmaceutical industry. We have a protocol for carcinogenicity that's virtually identical to the NTP,

although it does use different strains of animals.

The Lois Gold Carcinogen Potency Database that was developed at Berkeley. We use that.

IARC monographs.

The literature.

And I put this up. The EPA pesticide re-registration documents.

So I don't know if this group is familiar with it or not. But a lot of the information on pesticide studies is now up at the EPA website. And whenever there's a hit and a PDF file, we've used that information in billing our various QSAR models including carcinogenicity.

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DR. MATTHEWS: This is the weight of evidence given. And in terms of carcinogenicity, there's some chemicals out there that cause tumors in both rats and mice, and they cause multiple site tumors. In other words you just don't see tumor -- you know, a liver tumor. Or you find tumors in a variety of different organs.

And we are firm believers in the Ray Tennant paper. He published a paper on mutation research back in '93. And he basically put forward the hypothesis that the chemicals that have the highest potency, that is, the ones that really have these trans-species and multiple site tumors, are the ones most likely to be problematic in

humans. If you have a chemical that only had a single site response in two species and two gender of animals, the probability of that being a problem in humans is extraordinarily less in comparison.

So all of our QSAR models have used this kind of paradigm. Well, we'll give chemicals that -- you know, like an alkylating agent that just, you know, produces tumors everywhere in both genders and both species will get a score up in this range. For moderately potent toxins that have trans-gender single site tumor responses, we give them a little lesser activity.

And then for chemicals that, you know, had equivocal, inconsistent findings, et cetera, et cetera, we give them 20 to 29 and then our non-carcinogens found at the bottom.

Now, in terms of QSAR programs, you've got to decide where you're growing to draw the bar. And we essentially treat all of the chemicals with marginal findings as being inactive in a binary sense in order to be able to tell the QSAR program what's active and what isn't.

But we do keep track of the information on the specific activities of the chemicals.

In practice we've done many experiments to decide whether there's any biologic meaning in this group. And

all the experiments have been consistently negative. So everything that we've done has supported this hypothesis or weight of evidence.

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DR. MATTHEWS: In terms of the actual database, it's around 1600 chemicals. We have QSAR models for four software programs. There's actually seven models because you don't get exactly the same response when you put a chemical into mice and rats and male and female animals. The responses are often different. So we actually have models that represent the male and female animals and then a composite profile of what the carcinogenicity response was in that particular species.

And then of course the two expert systems.

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DR. MATTHEWS: Okay. So this is what the data looks like. We're going to -- first of all, I'm going to show you what it looks like when you take all positives from one or two QSAR programs.

You have a limited budget, so you picked one of the four programs. And then -- or you may have -- you know, you were able to afford two licenses. Well, this is the statistics for carcinogenicity.

In terms of specificity, you get a small drop in specificity by going to all the predictions of the two

programs, but not too bad. But you get a pretty substantial spike in terms of sensitivity. And those are the values that you'll see.

The other characteristics that we use to evaluate our models though, most people are familiar with the ROC -- that's the receiver operating coefficient. It's the sensitivity divided by false positives. And we found it very, very useful. Basically it's telling you that there's a high ratio of true positives to false positives with your program's predictions. And in addition to which you can do a Chi-square to see how well your program is predicting carcinogens versus non-carcinogens. So they're working very well.

In terms of coverage, as I said we -- the program's averaging around 95 percent or so. And the minute you put two programs together, your coverage actually jumps up to 100 percent.

It's really quite amazing. You can have chemicals that -- you know, you may have a multiCase program and it -- some parts of that molecule have got fragments that it's never seen before. So we treat that as a molecule. It's not covered by the program.

But on the other hand its three-dimensional -- two-dimensional molecular descriptor properties have been covered by other molecules that are in the data set. So

what happens is that when you put two of these programs together, you're actually able to predict almost all the organic chemicals that you put in. And so it really substantially improves the coverage of what you can do.

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DR. MATTHEWS: Okay. The other approach, as I said, if you really want to get the best possible predictions is to look at the consensus positives where you're predicting the same chemical to be positive. I mean what that really means is that there's something unique about the properties that -- let's say, a carcinogen that's really isolated from all the non-carcinogens in the database. There's molecular fragments, descriptors, et cetera.

And what happens is if you use any one program or two or three or all four in terms of specificity, this is what you get. So there's obviously a big drop in specificity by just using, you know, all four programs together, any one being a positive. The condition that we recommend is using any two out of the four.

In terms of sensitivity, you can see -- I mean at one extreme it's only about 16 percent. But then you're requiring every single program to make a correct prediction for that chemical for a different reason. So it's a really stringent criteria.

But the other extreme, you know, you're coming up with about 81 percent. So interesting enough, that means that there's really 20 percent out of the carcinogens that are in our database that even with these state-of-the-art programs they don't know why they're carcinogens.

These programs aren't foolproof. I mean they -- you know, they're going to get you this far, but they're not going to be able to get you all the way. And you can't be naive about this. I mean it just means that there are certain carcinogens that are poorly represented in the database and we just don't know why they're carcinogens and, you know, there aren't many examples of their molecular properties.

In terms of the ROC values, you can see an enormous difference depending on, you know, whether you're using one or all four programs.

And the Chi-square values. And I focus in on this one. This was actually the highest Chi-square value, and it was the reason that we actually ended up choosing this particular experimental condition. So we figure we can predict, you know, with specificity of 84 percent, roughly 60 percent of the carcinogens that are out there.

PANEL MEMBER BLANC: Can I ask a question?

DR. MATTHEWS: Yes.

PANEL MEMBER BLANC: From a public health

protective point of view, wouldn't you care more about sensitivity than specificity?

DR. MATTHEWS: Well, from a public health point of view -- in practice as a regulator, our confrontation is with pharmaceutical industry legal stuff. And ironically, you know, what you really need to do -- in our group, we get assignments now, and we have to pass this information on to our reviews. And we want to give them a substantial argument that they could use to either make a regulatory decision on the basis of those findings or request additional information from pharmaceutical industry.

So a prediction that's based on, you know, high specificity and there's convincing evidence in terms of the documentation that you could get for the studies that were the basis of that prediction, we really get into trouble. On the other hand, if you go forward with a prediction that has extraordinarily high sensitivity but poor specificity, there's a high probability that that prediction won't hold up. You won't be able to have a convincing argument for it.

So, you know, it would be nice if we had carcinogenicity studies for a hundred thousand chemicals. We don't. We've got it for 1500, and there's 200 million chemicals out there. So I think we're doing the best we

can with what we have.

But it's like the tip of an iceberg, and you have to -- you know, there isn't any solution to it. You can't test the 200 million chemicals. You can't do it. There aren't the resources to do it.

So this is, you know, our answer at getting closer to that target.

I don't know if I answered your question or not.

PANEL MEMBER BLANC: In a sense you did.

(Laughter.)

PANEL MEMBER BLANC: I mean my interpretation of your answer is that your goal is not to be public health protective; you have other priorities.

DR. MATTHEWS: Well, I've got a couple slides coming up where I think you'll see that in fact our motivation is extraordinarily public health protective. I mean there are areas that really haven't been addressed before.

Going on. In addition to, as I say, making a prediction, I think it's really important that you whenever possible link this to a specific mechanism of action. And what I have here is that in the DEREK for Windows program there's a rule -- mechanism of action rule that if you've got a thiouracil analogue, the program's going to tell you it's going to be a carcinogen. Well, it

turns out that in our database, none of the thiouracil analogues were genotoxic. Three of three were carcinogenic and they were all predicted by our programs.

In contrast, it has a rule for a genotoxic structural alert, the mechanism of action. And the full documentation is in there for that.

Well, it turns out that all of the aziridines in our database were genotoxic, they were carcinogenic, and they were predicted by the programs.

Yes.

PANEL MEMBER LANDOLPH: Can you also predict the potency as well from your programs?

DR. MATTHEWS: Potency in the sense that, okay, if it is a -- say, an alkylating fragment-like molecule, you know the relative potencies of all of the other alkylating fragment molecules in the database. So it would give you a score back in that sense.

If you're asking the question in terms of the dose at which it causes carcinogenicity, that's more complicated. But also you can get a prediction for that, because we have a model that predicts the actual dose at which you conduct the carcinogenicity study. And it's used as the top dose or the dose under which that you usually make your regulatory decision as calling it a carcinogen or not.

So you can predict the dose at which a chemical is carcinogenic as well as to whether it's liable to be a multiple-site carcinogen or have lesser activities.

CHAIRPERSON FROINES: Going back to our discussion from earlier today, and maybe we -- maybe we should hold questions. But just this -- can you take -- going back to the endosulfan discussion. Can you take the programs from metabolites and then ask the question which metabolites might be genotoxic and then from that you might then ask a question which compounds that have said "yes, yes" might be found to be carcinogen --

DR. MATTHEWS: Absolutely. In the multi-case program, the META program is fully automated. So what happens is that you put in your parent chemical and you have to specify how many levels you want to go in terms of metabolites. With pharmaceutical molecules, we just usually go first pass. But if you have some other indication or you want to know all possible metabolites, you can actually make this thing and go -- drive it down a carbon dioxide, you know.

It's not really a recommended thing to do.

But certainly you can predict these metabolites. And then the program exports these structures in an electronic format which it recognizes to make a prediction of toxicity. In other words it actually makes a mole file

or smile code representation of each of the metabolites that it predicts, and it does it automatically. So you automatically get the list of, you know, M1 to N15, whatever metabolites for your program. And then you can submit those back into the QSAR model that has the genetic toxicity that you're attempting to predict.

Now, the META program -- with the -- excuse me -- the Meteor program with DEREK you have to do it in two steps. It isn't automated. But it makes -- it gives you the electronic structures for the metabolites. But then you actually have to manually go in and take those out and then put them back into another system to make your predictions. But it's semi-automatic.

But, yes, you can. So you can say whether a metabolite is possibly genotoxic or not. And it will give you the mechanism by which it would be.

Yes.

PANEL MEMBER LANDOLPH: This would be an interesting prediction. You know, endosulfan, there's not real good carcinogenicity data. We're struggling with it. We think it's genotoxic. Could you predict that as one way or another, carcinogen or --

DR. MATTHEWS: I'm sure you could. You know, it's interesting. I'm kind of biting my tongue. But before I came here I looked endosulfan up in our

databases. And I got all my data from the re-registration document for endosulfan. And so I didn't get it from the public literature. I got it essentially from inside the U.S. EPA. And there was a carcinogenicity study there that was negative. And I don't know if that's the same one that -- you know, that you folks have been looking at or not. I don't know if you've looked at the re-registration document. Have you?

PANEL MEMBER HAMMOND: Tobi, behind you, saying yes.

DPR ASSISTANT DIRECTOR JONES: We use the same data.

DR. MATTHEWS: Same data. Okay.

All right. There was the positive study. And there was obviously, you know, findings in male reproductive studies. So in our models, you know, it was pretty much in line with what you have here.

I didn't attempt to do metabolites or anything like that. But, you know, it's quite doable.

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DR. MATTHEWS: Okay. Don't expect me to -- you know, to be able to read the lines in this. But basically the information that's in there is in a paper that's accepted for publication. And what it basically does, it has 15 rules that are in the DEREK program, making

predictions of carcinogenicity. Some were based upon genotoxic alerts, some were nongenotoxic. And the program -- our QSAR programs are able to predict about 223 out of 226. So it's like 98 percent of the carcinogens that fell into this group that had plausible mechanisms by which they cause cancer. So it's interesting.

In that program you're going to find a variety of rules for nongenotoxic carcinogenesis, which is sometimes -- it's not often times taken into consideration.

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DR. MATTHEWS: All right. I'm going to go through these fast. But if there's specific questions, you know, as I said --

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DR. MATTHEWS: -- we look at genetic toxicity endpoints and have a large database. We use three different programs. We don't focus in just on salmonella mutagenicity.

Now, this is an interesting list of endpoints. It's actually the genotoxic endpoints which in our one paper we found these data sets to be predictive of carcinogenicity. So we used these models to predict genotoxic activity.

Now, what you won't see on this list is an

endpoint such as cystochromistic change. What you don't see is the in vitro Chromo MAPs. Because in our hands, the data sets -- and these were very large data sets -- they didn't predict well carcinogenicity. Now, that's not to say that those aren't good gene tox tests. Actually SCE test is remarkable. You get the same chemicals, the four labs, and they always get the same answer. The trouble is it doesn't predict carcinogenicity.

But these are the endpoints that we use internally when we get an assignment to predict genetic toxicity.

PANEL MEMBER BYUS: Is that because of metabolism, do you think? Or is the QSAR only on the parent compound and doesn't address the metabolism? I'm following you, but I'm -- you see what I mean? That's --

DR. MATTHEWS: Yeah. There's obviously well documented cases where the parent molecule is not really the source of, you know, the mutagen.

But on the other hand, if you've got a fragment-based program, what it does is it goes and it identifies the region of the molecule that becomes the polar intermediate with points --

PANEL MEMBER BYUS: So in a sense it does adjust the metabolism?

DR. MATTHEWS: It does and it doesn't.

PANEL MEMBER BYUS: It does and it doesn't. Yeah, okay. Well, that's cool. That's a good question.

DR. MATTHEWS: What we haven't done -- and it's really important for you to know -- we have not invested a lot of time in the specific metabolites of the carcinogens in our database. And it's something we're actually going to do in this next year, because -- you know, as I said, 20 percent of those carcinogens aren't predicted. And it could very well be that the metabolites will answer a lot of those questions. We don't know. We haven't done it.

CHAIRPERSON FROINES: Well, it's a good -- it's an interesting issue because in southern California the polycyclic aromatic hydrocarbon that we breathe by a factor of 10,000 more than any other is naphthalene. And naphthalene's nongenotoxic. But -- and I hesitate to say this, but naphtha quinone is genotoxic.

(Laughter.)

CHAIRPERSON FROINES: And so that's an example, of which there are many.

I'm going to keep fighting my way through this group on this issue.

(Laughter.)

CHAIRPERSON FROINES: But in any case, there are a number of examples of metabolic pathways that take you to carcinogens that is not true for the parent.

DR. MATTHEWS: Right. And, you know, we're going to be looking at that. Although I have to tell you that the absolute majority, maybe as many as 90 percent of the pharmaceuticals that are carcinogens, well-documented carcinogens are all nongenotoxic. And their site of action is in endocrine organs. So the most likely explanation is pharmacologic overload. And that's got nothing to do with --

CHAIRPERSON FROINES: What is it in? What --

DR. MATTHEWS: They are chemicals -- they are pharmaceuticals that have caused tumors in endocrine organs, hormone-producing organs. So in other words something like the pancreas, the thyroid. And there absolutely is no evidence whatsoever that they're genotoxic. And, you know, you don't need to metabolize estradiol to make it a carcinogen.

So there probably are a lot of other mechanisms out there that are not going to be dependent upon metabolism. It might be important for some, but it's not going to be the answer for everyone.

PANEL MEMBER BYUS: Well, that was my question, kind of along the line tumor promotion. Do you model that at all?

DR. MATTHEWS: Never been able to do it.

PANEL MEMBER BYUS: You've never actually --

right. Okay.

DR. MATTHEWS: The control data set just isn't there. There hasn't been a standardized protocol. The data set is too small. We tried, but we can't do it.

CHAIRPERSON FROINES: Well, there are, for example, issues of gene methylation that have had a lot of research interest in recently and that -- but -- so that you talk about a nongenotoxic carcinogen, but in fact there are genetic changes that are occurring. And so one can't oversimplify the issue.

DR. MATTHEWS: Oh, absolutely.

CHAIRPERSON FROINES: So in a short-term test that would be negative. But in terms of the changes to the gene, they are significant. But they would be not picked up by any of the tests that people have traditionally used.

DR. MATTHEWS: This wasn't part of my talk. But I'm collaborating with an hepatotoxicity work group. The most common explanation for a pharmaceutical being taken off the market is hepatotoxicity. And it usually only takes a couple of patients, you know, with serious liver findings and liver disease. So our group -- yes.

PANEL MEMBER BLANC: I actually would take exception with that. It may be liver toxicity. But I don't think it takes a couple of patients. It depends on

what the mechanism is. If it's a truly ideosym --

DR. MATTHEWS: Operationally that's exactly what it's turned out to be. If you go down the list of about 50 drugs that have been taken off the market because of bad toxicity findings, that those particular case studies ended up being the pivotal decision -- pieces of information for the decision of either, you know, continuing the drug on the market in terms of having a black box or in fact discontinuing. And it usually was -- it amounted to just a few patients that had liver failure, that they were absolutely convinced I mean it was due to the particular pharmaceutical.

Why though? No one knows. Okay.

So one of the approaches that we're doing in our group is in fact to look at the gene arrays that are stimulated by these pharmaceuticals that have had severe hepatotoxicity. There's a group working on that.

Our particular group is going to go down the pathway of looking at specific metabolites. Since the metabolites of all the drugs taken off the market are known, it's one of the things that we're going to do next year, is look at that. That doesn't mean that we're going to get the answer with either one of these. But, you know --

CHAIRPERSON FROINES: Well, I think the gene

array work would be really interesting, because so much of it's been a fishing expedition up till now.

DR. MATTHEWS: Yeah. Well, this is really targeted. I mean you're going to get the answer one way or another. It's going to be "yes" or "no" and then you can move on.

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DR. MATTHEWS: Okay. Reproductive and developmental toxicity. This has represented about ten years' worth of work putting these data sets together and the QSAR programs.

We predict -- we have models for predicting reproductive toxicity in male and female animals, usually in both the rat and mouse. And then there's additional models for specific dysmorphogenesis or birth defects and behavioral toxicity. So that's what we use internally.

We have not been successful in predicting fetal growth and fetal death and some of the other parameters that are measured in those tests. For one reason or another they don't develop good QSARs.

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DR. MATTHEWS: Maximum tolerated dose. I had the question earlier, you know, can you --

PANEL MEMBER BYUS: This is not teratogenicity? This is just a --

DR. MATTHEWS: Teratogenicity.

PANEL MEMBER BYUS: Teratogenicity?

DR. MATTHEWS: Yeah, teratogenicity.

PANEL MEMBER BYUS: It's teratogenicity?

DR. MATTHEWS: Yeah.

PANEL MEMBER BYUS: Over -- we've had this -- or this developmental tox -- okay. That's good.

DR. MATTHEWS: Birth defects.

Yeah, there's a catalogue of about, I don't know, 800 of them. And that's specifically what we're talking about.

PANEL MEMBER BYUS: Got it.

DR. MATTHEWS: This is the models that we use to predict the dose at which a chemical -- you know, it could be a noncarcinogen or a carcinogen. But it's the dose that you would use to test for carcinogenicity. And as I said, the dose that usually ends up being the one that causes significant tumors is usually the top dose or the next dose down, which is about a third log down. So you can come fairly close with estimating what that dose is for carcinogenicity by putting these two systems together.

Those are the models for that.

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DR. MATTHEWS: Acute toxicity. We do have models for that, but they're old. And we really don't place much

need or interest in that particular area. So I'm going to move on.

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DR. MATTHEWS: Now, this one I wanted to talk about a little bit, because it's -- at the risk of getting on a bandwagon here. But I swear, every talk I give, somebody says, "Okay, yeah, that's really great. But what you're really using is animal data that predicts something that's in humans." And the answer is, no, we're not.

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DR. MATTHEWS: We're actually using data from post-markets of balance or clinical trials. It's not animals. We don't use any uncertainty or safety factor corrections. There's none required. This is the specific effect of the chemical on a person. And you do get out, you know, a milligrams per body weight her day number out of the system. And we use this to predict specific effects of chemicals on human organs.

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DR. MATTHEWS: Now, this is one particular data set. And I can actually point to one EPA organization that's using this approach. It's the Danish EPA. You know, I've been in touch with them. And they actually had this model, and they use this in their regulatory decision process, because they said what's really unique about this

is that the maximum recommended daily dose of a pharmaceutical -- when you go to the Physician's Desk Reference to the Dose Administration section, there's a dose in there that tells the physician, "Okay, you can't prescribe more than this on a 24-hour period to the patient" for whatever that medication is. And if you do -- you know, if accidentally the person takes more than that or you do do that, you're going to get adverse effects, sometimes very serious ones.

So it's essentially, you know, the threshold for toxicity in people. And this dose varies over about a ten-log range from, you know, your cardiac leukocytes that you treat arrhythmias for to -- you know, like an antibiotic where you take these huge horse pills, you know. It's absolutely amazing. So it's like a ten-log range. And, in fact, there's a structural basis for this. There's structural -- there's properties of molecules that tell you what this dose is.

So you can use these programs based on human data to give an estimate of what an organic chemical would be in humans.

Now, granted, this is all -- these are all pharmaceuticals. This is the basis of the database. So, you know, you're going to be able to predict plant-like substances, perhaps pesticides. But if you put in, you

know, a material -- you know, some of your typical EPA materials used to -- you know, like any oxidants or whatever, they're not going to be predicted because they're not pharmaceuticals. But anything that has -- but these programs will tell you whether it's covered or not, you know. And if it happens to be, you know, a borate or something that isn't predicted, it will tell you you can't make a prediction. But for other molecules it can. And it can give you a pretty reasonable number for a -- I think for, you know, a risk assessment scenario.

PANEL MEMBER BYUS: What about the COX-2 inhibitors, does it produce cardiotoxicity? How does that work out?

(Laughter.)

DR. MATTHEWS: We got this as an assignment.

PANEL MEMBER BYUS: Did you?

DR. MATTHEWS: Yeah, we -- actually Jim --

PANEL MEMBER BYUS: So if you're doing --

DR. MATTHEWS: -- and I attended the COX-2 inhibitor forum. And we were asked that question. And it's really interesting. Because, you know, if I were to put structures of 15 or 20 COX-2 inhibitors up there, you would see nothing in common with them. I mean it's everything from Tylenol to Vioxx. I mean they're really --

PANEL MEMBER BYUS: Well, they all have it, yeah. Different selectivities.

DR. MATTHEWS: Okay. But in a three-dimensional sense, there's only three receptor sites, in the COX-1, COX-2, and then there's kind of an amorphous binding that -- properties. So all of these molecules are fitting into the same three-dimensional receptor site. And the answer is you can -- with the program you actually have -- I hadn't planned on getting into this, but -- okay.

What Prous Science did is they actually had patent lawyers in all of the patent offices around the world. So they've got them sitting in Japan, the United States and Germany and everything. And the minute that the patent is filed, they collect all this information. And they have a model that predicts the mechanism of action of a pharmaceutical based on this patent information.

So what we did is we applied that model back against the COX-2 inhibitors, and it showed possible explanations for the cardiotoxicity. And it was something that worked -- you know, that wasn't in the literature.

CHAIRPERSON FROINES: I think my question is in fact exactly about this.

One of the things that's true about Cox inhibitors -- and in this case the one I'm raising is

aspirin -- is that if you're dealing with endothelial cells, the inhibition -- the regrowth of protein takes as long as seven days, eight days. And there's another site, which I'm for the moment blanking on, where the protein regrowth is of the order of minutes to hours. And so within the same mammalian species you have aspirin capable of inhibiting -- being a Cox inhibitor. But the rate of regrowth of protein is dramatically different. And so I think that the -- for example, that the endothelial cell slow regrowth has specific relevance to cardiotoxicity.

But can you look at that level of sophistication?

DR. MATTHEWS: Yes, you can, because it turns out there's only about 400 genes that control pharmacologic activity. It's not an infinite number. I mean most of their genes are doing something else entirely.

And most of these -- you know, a drug in the PDR tells you what the pharmaceutical company has documented for its efficacy and for one specific binding activity. But invariably each one of those pharmaceutical molecules probably binds to a half a dozen receptor sites. And we frankly think that's the basis of most of the adverse effects, you know. It's like -- you know, many antibiotics bind to the angiotensin receptor site. So they have ACE inhibitor like activity, you know.

And then -- you know, many of the antipsychotics

bind to the adeno receptor sites, so you have urinary incontinence. I mean, you know, it's all tied together.

PANEL MEMBER BLANC: Just clarify something for me in terms of the group of different software programs you're presenting the results for. When you present the results in terms of sensitivity and specificity and other predictive, it's ability to predict the characteristics of the known chemicals that were put into the database?

DR. MATTHEWS: That's right

PANEL MEMBER BLANC: So it's auto-predictive capability?

DR. MATTHEWS: Yeah.

PANEL MEMBER BLANC: Do you have prospective data for any of these in terms of what eventually turns out to be the case for chemicals which were not part of the data set originally?

DR. MATTHEWS: Well, we do for a couple of specific models. It turned out -- which I haven't gotten to. But there's a slide here about hepatotoxicity.

PANEL MEMBER BLANC: Well lets go to that then.

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DR. MATTHEWS: Okay, hepatotoxicity. So we have models where cholestatis, basic, you know, acute toxicity to the liver, liver enzymes, et cetera.

When we put this database together of around 1600

chemical, we thought we had the lion share of everything in the literature. Then we discovered a paper that summarized a bunch of drugs that had been taken off of the market in Europe. And there was a subset of about 25 drugs that were taken off because of liver findings.

And the statistics that we had for using the cross-validation LNO procedure were absolutely identical to the external for this data set. So that's -- and this has happened a couple of times.

On the other hand, its really easy to get your hands on 20 molecules that are very different, and then the predictions are not good. So it's kind of a Catch 22.

And to do the tests fairly you really need to have a balanced test set. So that it's not just, you know, 20 molecules that look the same and are all tremendously different.

PANEL MEMBER BLANC: Well, let me ask you a different question.

When you develop these tools, is it a typical process where you divide your data set in half, develop your predictive software, and then test it on the second half of your group?

DR. MATTHEWS: No. With the global QSARs we've never used that strategy. We've never had enough data. That's a classical procedure that works very well for a

Hansch equation, but it doesn't work for global, simply because instead of having, you know, one mechanism or one or two mechanisms being described in the equation, you probably -- how many mechanisms are there for carcinogenicity? There could be hundreds. So we've never had enough data. So we use all the data and then -- you know, on a yearly basis you may get 30 new chemicals. And of course we'll do an external validation and tests and see how well the model is. And occasionally we find something that's wrong with a model. You know, those new chemicals pouring out something that we didn't see, so we correct it.

But you can't do it that way.

PANEL MEMBER BLANC: No, I understand.

DR. MATTHEWS: Fifty percent doesn't work.

Well, if that's a limitation to them, I do think that one limitation then of the entire approach -- not limitation, but a context as we listen to this here is that what we're thinking about is how would you use these kinds of approaches for chemicals for which you don't already have the answer. And what you're doing is you're testing the -- you're doing the first step, which is a necessary first step, which is how does the model perform for those things for which we already have an answer? But until you're able to -- and it sounds like for your model

for hepatotoxicity you have been able to test it prospectively. But for most of these models you really haven't tested it prospectively in any true sense.

DR. MATTHEWS: We're using these QSAR tools for exactly the same purpose that you'd be using it to evaluate 250 air contaminants. We use it for contaminants in pharmaceutical preparations.

I mean pharmaceuticals don't come through a hundred percent clean. And, in fact, when they change the manufacturing process, you get a whole variety of other contaminants that are in there. Now, you can't sit down and reasonably expect a pharmaceutical company to synthesize large batches of each one of the contaminants and then perform a carcinogenicity study.

So what we do is we evaluate those contaminants and say, okay, based on the parent chemical and, you know, the activities of chemicals in a turning data set, there's no increased risk.

PANEL MEMBER BLANC: Yeah, but you haven't tested that because you have --

DR. MATTHEWS: No, of course. You can't, no, because it's the question of testing 200 million chemicals out there. You can't do it. You don't have the resources to do that.

PANEL MEMBER BLANC: I'm not criticizing what

you're doing. I'm just trying to make a point of its limitation. Until you have prospective data for how your predictive model performs, you're actually -- it's a heuristic exercise to an extent, isn't it?

DR. MATTHEWS: Yes, it is. And, you know, as I say, there have been occasions where -- I mean the very first paper that Joe and I published with carcinogenicity had an external validation test in there. And the statistics were identical to the model doing cross-validation. We actually had a set of about, I don't know, as I remember, 40 or 50 chemicals. They were the newest ones. It was in our very first paper in '98. So it did well.

CHAIRPERSON FROINES: Okay.

PANEL MEMBER HAMMOND: If I'm understanding you correctly -- and this is following along with Paul's ideas -- you build these models and they're based -- they have some underlying mechanism of action. So I'm going to be very simplistic. Let's just say one class of models is working on the basis of alkylating agents and another class may be basing on some sort of three-dimensional, you know, shape. You know, just those two kind of things. And you've got sets of models for each of those and you're bringing all those different kinds of models together and looking, right?

DR. MATTHEWS: (Nods head.)

PANEL MEMBER HAMMOND: And then as long as we're talking about molecules that have alkylating agents that are alkylating or they have some stereochemistry or some three-dimensional shape that fits these, they'll be good predictors. What would seem useful to me, and perhaps you have this to build into it, is to say, okay, the underlying things that are driving our models are these factors -- I'm being simplistic now, but alkylating agent, electrophilicity, whatever. Then it would seem to me you -- if you -- your problem with these chemicals you found in Europe in this paper that just were outside of the realm of these models -- it would be useful if you had a way that you could take a chemical and put it in and say, "How well does this molecule fall into the models that this has been dealing with?" So in other words, if the system could say to you this chemical is outside of the range of possibly to be predicted, that would be very helpful in and of itself, as distinct from, you know, this is in the realm of good prediction.

DR. MATTHEWS: Actually that's an absolutely terrific idea. And I think that the May version of MultiCASE will actually enable you to do that. I've been asking. And they've been developing a procedure where you can put one molecule back in at a time and assess how well

it fits into the overall model and at the specific clusters within that model. Because there's always the question of whether you accidentally, you know, incorrectly scored something and put in, you know, a false positive or a false negative into your training data set; or in fact it was just a bad experiment. You know, it was a negative. And if you really went back, you know, they never reached the maximum tolerated dose, you know, with that chemical.

PANEL MEMBER HAMMOND: I guess I'm kind of saying --

DR. MATTHEWS: In fact, it probably was a carcinogen.

PANEL MEMBER HAMMOND: Yeah, I'm saying -- we understand that you can't do everything yet. You can't predict everything yet. We'd all be --

DR. MATTHEWS: No.

PANEL MEMBER HAMMOND: But this is wonderful to be moving towards it. But to be able to understand when we're getting outside of the realm of the power of the models to make a believable, credible prediction, just knowing that would be very useful.

DR. MATTHEWS: Well, that's what coverage is all about. In other words it's the domain of applicability, that's -- the OECD has a document on how you're supposed

to do QSAR research and all the principles. And one of them, which is to assess that domain and whether your molecule is part of it or not. So each one of these programs uses a different paradigm for that. But --

PANEL MEMBER HAMMOND: -- but it will give you that?

DR. MATTHEWS: -- it will tell you that, oh, yeah.

PANEL MEMBER HAMMOND: So that you can actually -- those 20 compounds from Europe that were you talking about -- now, that was hepatotoxicity, I think.

DR. MATTHEWS: Yeah.

PANEL MEMBER HAMMOND: But those -- the program could also come out and say, "We're not really well suited to predict these chemicals" --

DR. MATTHEWS: Absolutely, yeah.

PANEL MEMBER HAMMOND: -- as distinct from saying, "Oh, these are safe"?

DR. MATTHEWS: No, no. It would -- and, in fact, you know, I mean when you put like a Toska data set through some of these models, they say, "Oh, my God, what in the world is this?"

PANEL MEMBER HAMMOND: Somehow because it was generated from pharmaceut -- because the data set -- because those models were generated from pharmaceuticals,

right?

DR. MATTHEWS: Yeah. I mean it's out of pharmaceutical molecule --

PANEL MEMBER BLANC: And of the -- in something like this with the hepatobiliary effects where you have 120,419 study records, those would actually be cases within case reports?

DR. MATTHEWS: Patient reports, yes.

PANEL MEMBER BLANC: So this would be patient reports?

DR. MATTHEWS: Yeah.

PANEL MEMBER BLANC: So, for example, if a case series had ten patients, that would count as ten study records?

DR. MATTHEWS: Yes.

PANEL MEMBER BLANC: That's why the numbers are so much higher than the number of chemicals?

DR. MATTHEWS: That's right. The overall database is actually about ten million. It represents every patient report that's come in at our Med Watch program since 1969. So it's actually ten million.

PANEL MEMBER BLANC: So for this program this is completely derived from Med Watch, for example?

DR. MATTHEWS: Yes. Well, no.

PANEL MEMBER BLANC: Or would it also be cases

published in the literature that --

DR. MATTHEWS: That's exactly right.

PANEL MEMBER BLANC: -- that weren't ever in Med Watch?

DR. MATTHEWS: But Med Watch doesn't take into account drugs that have failed in Europe. And it's a serious deficiency. There's a lot of drugs that never get marketed here, but they have the same type of findings. So, you know, we knew that was important from QSAR's perspective, so we actually reviewed the literature as well as the Med Watch. So both of them are in there.

PANEL MEMBER BLANC: Okay. And the same thing would be true of the next slide with the urinary tract?

DR. MATTHEWS: Yeah. Urinary tract, yeah. There's a kidney and bladder.

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DR. MATTHEWS: And I got to put up this slide simply because it's a UC Berkeley. Anna is doing this whole thing. She's absolutely remarkable. This is her -- she calls it her firstborn child. But she has literally put this thing together. She has captured all of the Med Watch patient reports from our old spontaneous reporting system, and then the MERS system that we're using right now. She's reviewed the literature. And she's into her second QSAR program as we speak. So I mean it's just

amazing. That's what she's doing.

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DR. MATTHEWS: Oh, let me go to the very last slide.

There's a series of publications. But this is a website. And it has a list of our publications and things and the web links to the various QSAR programs.

Okay. I'm sorry I took so long.

CHAIRPERSON FROINES: If someone wants to use either EPA or your QSAR efforts, if one had questions, do we have to then go buy or get site licenses of one kind or another? Or is it something that one can go to EPA or FDA for --

DR. MATTHEWS: All of the EPA programs are for free. So you could immediately -- your organization could immediately get the OECD QSAR toolbox, which is more than just QSAR tools. It actually has a Norris data set in there. I mean it would be really helpful for most of your projects. In addition to which the EPA's suite of programs is free and they have training. So, you know, it's easy to contact their people.

CHAIRPERSON FROINES: Well, like for the metabolism program.

DR. MATTHEWS: Oh. Now, the other two -- you know, you have to kind of -- no, the other ones are not.

Our program -- our research is not really supported by the center. I mean we get a little bit of money. But we've supported it through leveraging with agreements with software companies. I mean they have to modify the programs and they have to help us out at each step of the way. And then we get a small contribution back that we use to keep building the training a data set.

So the licenses for these programs vary tremendously. And it depends on, you know, what you think your needs are going to be. The prices are coming down though because it's getting competitive.

CHAIRPERSON FROINES: Does OEHHA --

PANEL MEMBER BYUS: What are we talking about?

DR. MATTHEWS: You know, I honestly don't know. I mean I try -- in fact, I make it a point not to know, because I don't want to get into that discussion.

They're all small companies, so they -- you know, there's deals that can be made.

(Laughter.)

CHAIRPERSON FROINES: Does OEHHA have --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Money?

(Laughter.)

CHAIRPERSON FROINES: No, I know what you have moneywise. And that's --

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: It's pretty sad.

PANEL MEMBER HAMMOND: Could we call that supporting small company development, small business in California? Do it that way?

(Laughter.)

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Yeah. We actually are -- we have the EPA suite of software because it's available on line. And in January -- mid-January we're sending a dozen staff to be trained in the use of the EPA QSAR software. So there's some of that. But it doesn't -- they're more -- less the global software and more the narrower congener-based software applications. So it's --

CHAIRPERSON FROINES: Well, that's good.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Yeah. And we're looking into the OECD package too because it's got more global inputs than the EPA packages.

CHAIRPERSON FROINES: Are there other questions for Ed at this point?

PANEL MEMBER BLANC: Well, I just would reemphasize that I think that in this kind of presentation it would be really interesting for us -- and maybe you could send a couple of slides out just by e-mail to Peter

that he could distribute on the specific results that you've had that you refer to when you did your validation testing on external supplemental groups of chemicals. I think that would be very interesting, if you have any -- I don't --

DR. MATTHEWS: It's in the papers.

PANEL MEMBER BLANC: Well, I don't want you to make prepared slides. But if you already have them somewhere else --

DR. MATTHEWS: Actually I'd prefer that you actually went to the individual publication, because it has all the details and it has the actual names of the chemicals and the ones that are used.

Now, the hepatotoxicity paper is not out yet, but it will be out next year. But I have some external validation studies. As I say, usually we can't do that. There just isn't enough data. But we try to whenever we can.

CHAIRPERSON FROINES: Gary.

PANEL MEMBER FRIEDMAN: Have you looked at any chemicals that are in herbal remedies, or is the FDA not allowed to do that?

DR. MATTHEWS: Well, Congress doesn't want us messing in that area. That's the simple way to answer your question.

Actually, the new fella that's on the list, Luis Valerio, that's his personal interest. He's a pharmacologist. And he has a couple of ongoing research relationships, one of which involves herbal -- actually it's dietary -- herb --

PANEL MEMBER FRIEDMAN: Dietary supplements?

DR. MATTHEWS: Dietary supplements. It's not herbal. But it took -- it's hard to distinguish the two, frankly, because they're all plant substances.

PANEL MEMBER FRIEDMAN: Yeah, I wasn't sure even what to call it.

DR. MATTHEWS: Yeah. So there's an institute in Mississippi that's really at the forefront of that. And we may get involved with that.

CHAIRPERSON FROINES: Thank you very much.

DR. MATTHEWS: You're welcome.

CHAIRPERSON FROINES: Very pleased. And you'll hear from us again.

(Laughter.)

CHAIRPERSON FROINES: So this is good. I should have given my talk after you and then we could have compared results.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: John, go ahead if you want.

CHAIRPERSON FROINES: No, no. Believe me. I was

so beaten up last night on this subject, that I'm happy to wait till February.

(Laughter.)

CHAIRPERSON FROINES: Go ahead.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Okay. I just developed a really few slide and I'm going to go through them pretty quickly and probably skip a few in the interests of time.

But you will hear shortly from ARB on the prioritization method they've been using and the changes they're proposing to look at chemicals as potential candidate toxic air contaminants. And I just developed a few thoughts after talking with Dr. Froines on things that could happen in the future.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: And I just wanted to remind the Panel that we did a prioritization of toxic -- I already identified toxic air contaminants that we thought may disproportionately impact kids back in 2001. And we used a consideration of exposure looking at what data there are available for ambient air measurements, emission inventories, both mobile and stationary, to consider

whether there's widespread exposures. So that's one piece of a prioritization: Is it out there? And is there a lot of exposure?

We also considered the toxicity of the compound in light of its susceptibility of immature organisms. So that was another important component of that prioritization, because you don't always have the data that you want on exposure or toxicity.

And then the other thing we did was we had a ranking of the chemical by toxicity and exposure, where those data were available. So things got attention by virtue of 2 and 3, which are not -- I realize it says 1 through 2.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: And also to remind you --

PANEL MEMBER BYUS: Just how you said priorities. Never mind.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: So George actually mentioned these earlier today, that we had toxicological endpoints that we think raise flags when you're talking about exposure to immature organisms, including obviously developmental tox, neurotox, endocrine disruption, immuno, respiratory -- and we included asthma in that -- gene tox, and

carcinogenicity. And as you'll hear in a minute, these considerations have now been incorporated into ARB's prioritization strategy.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Then as I mentioned earlier before Ed gave his talk, we have been looking at how other organizations have looked at large lists of chemicals and moved things up to the top of concern for potential action. Environment and Health Canada, both agencies, were mandated under the Canadian Environmental Protection Act to look at all the chemicals in commerce in Canada and to prioritize them so that there can be some actions towards the chemicals of most concern.

So they actually looked at 23,000 substances and developed this prior paradigm by which to prioritize. They considered the greatest potential for exposure. So they had information that fed into that, including persistence and bioaccumulation. And they considered where the chemicals were toxic, either in humans or if they had -- they focused also a lot on the environmental wildlife -- impacts on wildlife. So they looked at nonhuman organisms too.

And then this categorization essentially represented a priority-setting exercise so that they could

systematically identify substances that should be looked into more closely for screening assessments and possibly control strategies. And this kind of thinking is relevant to looking at candidate TACs.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH

MANAGER MARTY: So I just wanted to note they had specific criteria in their prioritization for persistence in various media and for measurements of bioaccumulation. And then that third bullet is for aquatic tox. So they had cutoff criteria. If the chemical, the LC50, was below one milligram per liter, it went into a separate bin and so forth.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH

MANAGER MARTY: So actually their prioritization results are available on CD, and I now have a copy of that. And I did want to point out that they used different -- they used tools that they developed themselves. This took seven years and 60 PY. So just to give you an idea as to what we were talking about in terms of resources.

Yeah, I'm not sure that we have that many people in OEHHA.

So I wanted to mention that they developed exposure tools and they also had hazard tools that they

use. So we can look at these things and say, wow, can we look -- can we use any of this type of information? And they also used quantitative structure activity models.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH

MANAGER MARTY: Their simple exposure too was just a relative ranking by which substances were binned on the amount produced in Canada -- the number of produces and the amount imported as well and uses.

So for uses they looked at, you know, do people use it like right up close in their face? Is this like a solvent that you would use? And that they weighed heavily actually in their prioritization. So that was interesting.

Then they had more complex exposure tool, which they called the ComET, which looked at basically fugacity modeling. So I believe it was Don Mackay that did most of this work. And to provide bounding estimates of both consumer exposure, what they termed nearfield, and multimedia exposure of the general populations, which they term farfield.

And they actually had by age group in there too. So they considered that kids have different activities. And so we're going to take a look at how they did all that.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Note a couple different hazard tools. One was they called the simple hazard tool. And basically they just ran through other organizations' groupings of genotoxicants, repro, carcinogens, developmental. And they did look at Prop 65, and I should have put it on here.

And their assessments, they selected various assessments from these different based on the comprehensiveness of the review and whether it had been peer reviewed.

So that was their simple hazard tool just as a first cut.

Are any of these chemicals on these other lists?

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Then for their more complex hazard tool they looked at specific endpoints and specific information sources. And here's where their QSAR came in. So they used QSAR tools to look at carcinogenicity and gene tox, developmental tox, and then chronic and cute tox.

They also where they had data set criteria for binning the compounds into high versus medium or low hazard. And if the NOAELs, for example, for repro tox

were less than or equal to ten milligrams per kilogram day, it went into a higher concern category. So my point really is is that they developed specific criterion by which to do this analysis.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Ed talked about the FDA tools. And he did mention that EPA has a lot of tools for screening. And we couldn't -- unfortunately we couldn't get the folks we really wanted to out here because there's apparently a big meeting in Paris that they're all going to.

We should have gone there. What were we thinking?

So, anyway, they do have QSAR-predictive tox models --

PANEL MEMBER BYUS: We've got Ed.

(Laughter.)

PANEL MEMBER BYUS: Ed, thank you very much. Really outstanding presentation.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: So Ed mentioned oncologic, which came out of EPA.

ECOSAR is one that actually focuses on nonhuman endpoints. So they look at ecologic toxicity data and they have these quantitative SAR models for that.

And then they also use exposure models. So they have somewhat -- relatively crude actually exposure models. But, you know, you got to do what you got to do. And they're all on the web and you can get those.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: I'm going to skip that one. And Ed already talked about that.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Well, let's go over to some suggestions that we've been batting around at OEHHA. One came actually out of a conversation with Dr. Atkinson where we mentioned this atmospheric transformation model at the University of Leeds. And we thought, hey, would it not be fun to take a couple of compounds, run them through this University of Leeds model, and then take all the products -- and apparently it runs it through to basically the end of its possible transformation -- and then take all those products and run them through QSAR models. So that was kind of a fun idea that we had.

The other thing that we obviously should be doing is looking at the OEHHA gasoline document that Lauren Zeise and Sara Hoover and crew put together. And there are compounds identified in that document as atmospheric

transformation products from gasoline emission chemicals.

U.S. EPA has looked at high production volume chemicals, and they now have gathered a whole bunch of data on those chemicals and are putting it all together. And it's available publicly. We should look at those chemicals and see what they're saying about toxicology of those chemicals.

And then also look at the chemicals identified as high use in Canada or high concern and see if there's anything we can glean from those programs.

And then already ARB asks the districts, do you guys have any chemicals that you're concerned about from specific sources? So that already is incorporated.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: So another couple of suggestions. OEHHA evaluates identified chemicals, not just through the literature. I would see that would be one thing we would do is look immediately what do we know about this chemical. But also can we use any QSAR models to flag some of these things as chemicals that we should be concerned about.

And I mentioned we're having some training and we're looking at the OECD models. And this would result in bringing more information to bear than we currently do,

one prioritizing candidate TACs.

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OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH

MANAGER MARTY: And I -- am I going backwards? I mentioned that we should evaluate the Canadian prioritization process and look closely at what they did and what they managed to gather, which is actually all on their website. And every three months they're putting up an additional 15 toxicology profiles for their identified chemicals of concern. And also the HPV.

So it's and well and good to flag chemicals of concern. But you still have to go through the whole regulatory process. And you're always going to run into this issue, is there enough data to use to identify a chemical as a TAC? Is there exposure data? Can we actually even measure the chemical? Is there analytic methodologies for some of these atmospheric transformation products that we know are probably out there but we don't know the levels?

And in terms of toxicity data, you know, we've never been so bold as try to base a regulatory decision on a QSAR model. So, you know, they're not necessarily going to tell you that something is not a bad actor. But there may be plenty of flags for a chemical or two that it is a bad actor, yet you lack the animal study. So what -- it

brings into -- it begs the question, what do you do with those?

And then the other thought we had was can't we move more towards identifying classes with related toxicity? And we've talked about this before. We've done it before. We have the dioxy polychlorinated dibenzo dioxin furans and the PCB congeners identified as groups. We identified ETS and diesel. So I think it's probably something that we could work a little more towards.

So that's all I had to add.

DR. MATTHEWS: What took us so long in getting to where we are right now is in putting together the chemical structures is in putting the chemical structures together into a database. And now that's -- you know, if you were to start today, you could get your hands on the Toska database from U.S. EPA, you can get -- you know, and it would have the smile codes or mole files. You can get from the Danish EPA the data set that's being used in the OECD right now. That's about 176,000 chemicals. You know, all of this information is out there. And, you know, believe me, when you can knock that off as one of the tasks you don't do, and if you can go through your toxic air contaminants, if you're looking at a list of 250, you would have already had virtually all of the structures and, furthermore, a lot of structures of

chemicals very similar to them. So, you know, right off the base you'd be able to start with a powerful, powerful data set for that project. And they're out there. They're freely available.

CHAIRPERSON FROINES: I'm a little confused, because I read the GAO study on Toska, which is very devastating to say the least. And the implication from the GAO study on Toska was that one of the major problems with Toska has been the lack of accessibility to data which has been kept confidential for business purposes.

DR. MATTHEWS: No. What I'm talking about is the chemical structures, not the actual toxicologic data.

But, believe me, that ends up being a tremendous, tremendous task getting all those structures right, you know, the right confirmations, et cetera, et cetera, It's an enormous task. We have a chemist that that's -- she spends all her time doing this, trying to get it right.

And, you know, you can get the data set from -- the Canadians have offered that up. The Danish EPA has their data set. So I mean overnight you could have a data set of 200,000 chemicals, which would cover just about anything that you're going to run into. And, as I say also, you know, very similar chemicals as well.

CHAIRPERSON FROINES: Okay. Melanie, just as a complete aside. I'm on an expert panel in Canada for

Health Canada and we're looking at the statistics and the availability of all the data in Canada on health outcomes. And it would be very interesting at some point to take what we're doing and what you are doing and see if we could connect any of that. This will be on all health data for the entire country. So we'll see.

Questions for Melanie?

PANEL MEMBER BLANC: Melanie, you didn't mention Reach. Do you think there's something a apropos for that?

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Yeah. Reach is not yet implemented. They just started implementation this past summer. And when they get information compiled that they can put out there, then we will definitely look at it. They do already have a criterion for persistence and bioaccumulatives.

CHAIRPERSON FROINES: In the document that we're writing for the state, for Cal EPA, we are going to argue that Reach is looking at too limited a number of outcome measures and that OEHHA should be able to -- should be able to look at multiple outcome measures in terms of prioritization for green chemistry purposes, that there -- we think that one should look at ten outcome measures and not three -- or more.

PANEL MEMBER BLANC: Oh, I think it's going to be the case will all of these things, that it's -- it's when

something appears on one of the lists that you're interested in. It's not so much that if it doesn't appear on their list, you're home free. And if it appears on multiple lists, it makes your task that much easier.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Yes.

CHAIRPERSON FROINES: Looks like we have -- you slipped by without giving us a list. But I guess we'll let you go because you're obviously not ready to do that. But it would be really nice to see some chemicals on the board.

(Laughter.)

CHAIRPERSON FROINES: Thanks, Melanie.

I think we have time for ARB. I think you and I are going to present next time. And I know you predicted it, and I was more optimistic.

Melanie, I think it would be useful sometime in the future to have a session that went on for an hour or so, two hours, that would deal with the Lauren Zeise toxicity testing NAS report, because I don't think the Panel is necessarily familiar with that. And I think that would be -- the issue is what are the endpoints that are useful and high throughput assays and other approaches.

And the question for us obviously is: Are they validated, can they be used -- are they mature enough to

be used in a regulatory context? And so maybe Lauren could come and tell us.

OEHHA AIR TOXICOLOGY & EPIDEMIOLOGY BRANCH MANAGER MARTY: Sure.

(Thereupon an overhead presentation was Presented as follows.)

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: As we're getting ready for our presentation, let me just make some -- Oh, I'm sorry.

My name is Jim Aguila, Manager of the Substance Evaluation Section. And Peter's passing out a packet to each of you.

I'll just point out that we're just going to go ahead and go into the presentation. The other documents that are included in your packet are basically serving as more detailed backup documents that we could use if you wanted to have a more substantive conversation on some of the items.

CHAIRPERSON FROINES: Can I ask you a question?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Absolutely.

CHAIRPERSON FROINES: I'd like to close the meeting about 3:15 for people's travel time. Do you think you'll be more than a half hour?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

No, our presentation takes about 15 minutes.

CHAIRPERSON FROINES: Because, otherwise, I think Tobi would be shorter than you.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

Our presentation takes about 15, 20 minutes.

CHAIRPERSON FROINES: Okay. And then if we need to, we can bring you back at the next meeting just to finish up.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

Okay. So it's okay to proceed then, Dr. Froines?

CHAIRPERSON FROINES: Absolutely.

Okay. Well, I'll go ahead and introduce Susie Chung of our staff to give the presentation.

CHAIRPERSON FROINES: No, I see her e-mails all the time.

(Laughter.)

ARB AIR POLLUTION SPECIALIST CHUNG: Good afternoon.

Good afternoon, Dr. Froines and members of the Scientific Review Panel. I'm Susie Chung of the Substance Evaluation Section at the Air Resources Board.

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ARB AIR POLLUTION SPECIALIST CHUNG: In today's presentation, I'll begin with some background on our efforts to prepare a toxic air contaminants identification

program plan and then give you an overview of the 1993 priority setting methodology.

Next I will introduce the proposed priority setting methodology that we would use in the plan update, and to follow up with a discussion of the basis and point assignments.

I will then review some examples of the results we obtained using the proposed methodology to rank the candidate toxic air contaminant and currently listed toxic air contaminants.

I'll conclude with our plans for future work.

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ARB AIR POLLUTION SPECIALIST CHUNG: I'll begin with the background information on the Toxic Air Contaminants Identification Program Plan, and then move on to the Air Resources Board's Toxic Air Contaminants Program framework.

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CHAIRPERSON FROINES: That wasn't an indication that you're going to take up isoprene from trees?

(Laughter.)

ARB AIR POLLUTION SPECIALIST CHUNG: In January of this year we talked to you about a schedule for preparing a toxic air contaminants identification program plan. This slide shows the evidence of the plan.

We worked with the Office of the Environmental Health Hazard Assessment and together completed a draft of the first item, updated priority setting methodology. This work is the focus of today's presentation.

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ARB AIR POLLUTION SPECIALIST CHUNG: This slide shows the process outlined in state law for the identification of toxic air contaminants. As you can see from the flow chart, the process begins with the priority setting and selection of a substance of concern.

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ARB AIR POLLUTION SPECIALIST CHUNG: This slide shows the steps in the risk management process. Once a substance is identified by regulation as a toxic air contaminant, the law requires us to -- this process to assess the need for further risk reduction measures.

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ARB AIR POLLUTION SPECIALIST CHUNG: Returning to the priority setting step in the toxic air contaminant identification phase of the program, state law requires us to consider the factors shown here.

CHAIRPERSON FROINES: Can I ask you a question?

The actual definition in the law, I don't remember -- you put risk of harm to public health. Does anybody remember what it actually says? Because it's --

the reason I raise it is that it's fairly broad in scope. And I just wanted to remind the Panel of --

ARB AIR QUALITY MEASURES BRANCH CHIEF BROOKS:

The definition of toxic air contaminant is broader. And I can read that to you.

"Toxic air contaminant means an air pollutant which may cause or contribute to an increase in mortality or in serious illness or which may pose a present or potential hazard to human health."

And then it goes on to say that a substance that's listed as a hazardous air pollutant by the federal government is also included.

CHAIRPERSON FROINES: So the Panel should be aware of how broad the definition is. Because it may -- over time it may have been -- so please continue.

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ARB AIR POLLUTION SPECIALIST CHUNG: I'll now discuss the 1993 priority setting methodology.

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ARB AIR POLLUTION SPECIALIST CHUNG: For purposes of the Toxic Air Contaminant Identification Program, the methodology as screening tool serves two main functions:

First, it is a screening tool used to rank -- so the system may have high, medium, or low impact on public health in California. This serves as the technical basis

for recommendation on which candidate toxic air contaminants should be considered for formal identification as a toxic air contaminant in California.

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The methodologies also tool they would use rank the substance that are already on toxic air contaminants list to identify substances that may need health value for risk management.

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ARB AIR POLLUTION SPECIALIST CHUNG: The priority setting methodology used over the years was originally approved by the Scientific Review Panel in 1990 and revised in 1993. In the 1993 methodology there were eight categories in which a substance could be already awarded up to 40 points.

The eight categories are used to characterize the range of cancer and non-cancer health effects a substance is reported to have, as well as the extent of a public exposure to the substance.

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ARB AIR POLLUTION SPECIALIST CHUNG: After having some experience with the 1993 methodology, we concluded that a number of changes should be made as shown on this slide.

As part of the review, we considered new

legislation requiring have to account for impacts to children's health as well as the availability of reputable health impact information that we can consider in the priority-setting process.

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ARB AIR POLLUTION SPECIALIST CHUNG: I'll now discuss our proposed priority setting methodology.

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ARB AIR POLLUTION SPECIALIST CHUNG: Today we're proposing a number of changes to the 1993 methodology. This revised approach is nine categories, worth a total of 36 points.

The main element of the 1993 methodology, cancer health effects, non-cancer health effects, and the exposure parameters remains as the fundamental criteria for evaluating a substance's potential public health impact in California.

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ARB AIR POLLUTION SPECIALIST CHUNG: In the following slides I'll discuss the basis and point assignments for the categories in the proposed methodology.

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ARB AIR POLLUTION SPECIALIST CHUNG: The cancer classification category serves the same function as it did

before. However, we propose to add consideration of the studies conducted by the National Toxicology Program.

In the proposed methodology, substances have either a high, medium, or low cancer potential. Substances with a high potential include the compounds that are known probable or possible human carcinogens by the U.S. Environmental Protection Agency or International Agency for Research on Cancer, or if there's a clear evidence that they are carcinogenic by the National Toxicology Program.

Substances that are unclassifiable by the U.S. Environmental Protection Agency or International Agency for Research on Cancer or have some evidence of carcinogenicity by the National Toxicology Program receive 2 points. If no data exists or for a compound with no or low carcinogenic potential, 0 points will be assigned.

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ARB AIR POLLUTION SPECIALIST CHUNG: This category allocates points for substances based on the number of organ systems having adverse non-cancer health effects. No changes are proposed for this category.

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ARB AIR POLLUTION SPECIALIST CHUNG: This category serves to account for non-cancer chronic, acute, or reproductive effects in adults.

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ARB AIR POLLUTION SPECIALIST CHUNG: We're proposing the addition of a children's health category. For this category, staff from the Office of Environmental Health Hazard Assessment have recommended that the criteria for point assignments be based on evidence of the eight cancer or non-cancer effects listed in this slide.

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ARB AIR POLLUTION SPECIALIST CHUNG: In this proposed methodology, points should be assigned as shown here.

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ARB AIR POLLUTION SPECIALIST CHUNG: In this category, up to 2 points can be awarded to substances that persist or bioaccumulate. The log of KOW or a long biological half life of a substance was not specifically considered in the 1993 methodology.

CHAIRPERSON FROINES: Can I ask you a question?

Let's take lead, for example. And it would be under number of organ systems adversely affected, presumably. And in all your categories you're talking about the number of systems that are affected. But if I were making a decision about whether to bring lead to the panel as the TAC, I would immediately throw out renal effects, because you don't see renal effects until the

person's almost got no kidneys left. And I would -- and heme synthesis impairment is reversible upon leaving the workplace. And so what you would make your decision on with lead of course would be neurologic effects. And so the danger in what you're doing here is --

PANEL MEMBER BYUS: Cardiovascular.

CHAIRPERSON FROINES: What?

PANEL MEMBER BYUS: But that's one of the things we made our decision on, was the cardiovascular effects. Hypertension

CHAIRPERSON FROINES: Oh, yeah. Okay, okay. So you -- no, but the point is --

PANEL MEMBER BYUS: So it's only -- It's not just neuro.

CHAIRPERSON FROINES: The point is, if you have -- if you have two systems affected -- I'll buy -- you know, we could list a million things with --

PANEL MEMBER BYUS: But I mean we actually did make decisions on that based on --

CHAIRPERSON FROINES: Okay. So let me just agree that we have two systems affected. But we would clearly put -- have to have a way to put lead way up because of the neurologic consequences in children.

So the danger of having it based on number of systems affected is that it doesn't deal with severity.

PANEL MEMBER BLANC: Isn't that -- if I understand it correctly -- haven't gotten that far, I guess. But your comments health score is partly to allow some of that qualitative sense to be factored in, is that the goal of that?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

Dr. Blanc -- yeah, this is Jim Aguila.

Dr. Blanc, that's correct. Actually lead under our current prioritization would receive 4 points. But in addition to that we also have accounted for severity of heath effects in the "comment" column, as you mentioned.

CHAIRPERSON FROINES: In the what? Where --

PANEL MEMBER BLANC: The final column, that's health -- comments health score.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

Dr. Froines, we're jumping a little bit ahead. We're actually going to cover that.

CHAIRPERSON FROINES: No, don't worry. Go ahead. I'm sorry I raised it. I don't mean to take your time.

ARB AIR POLLUTION SPECIALIST CHUNG: Okay. We'll continue with this.

In this category, up to 2 points can be awarded to substances that persist or bioaccumulate. The log of KOW or a long biological half life of a substance was not specifically considered in the 1993 methodology. Note

that for assigning points in this category the persistent bioaccumulative toxic profiler or a PTB Profiler would be used.

The PBT Profiler is a program available from the U.S. Environmental Protection Agency that uses computer estimation methods to identify persistent bioaccumulative and toxic chemicals based on chemical structure and physical chemical properties.

It then compares these results with a well-defined set of criteria for these three category to identify chemicals that exceed the criteria threshold.

The PBT Profiler is an example of a quantitative structure activity relationship model.

PANEL MEMBER FRIEDMAN: Could you explain what you mean by log KOW equals 2 -- parenthesis, Log KOW value is greater than 3? I don't understand how the "greater than 3" relates to the 2.

ARB AIR POLLUTION SPECIALIST CHUNG: Log KOW -- this is number of point system --

PANEL MEMBER BLANC: You'd get 2 points if you had the log greater than 3.

PANEL MEMBER FRIEDMAN: Oh, I see.

PANEL MEMBER BLANC: It's the weighting system.

PANEL MEMBER FRIEDMAN: Oh, okay.

And is KOW the half life?

PANEL MEMBER ATKINSON: No, it's a nocturnal water partition coefficient.

PANEL MEMBER FRIEDMAN: Beg your pardon?

PANEL MEMBER ATKINSON: It's a nocturnal water partition coefficient.

PANEL MEMBER FRIEDMAN: Oh, I have no idea what that is.

PANEL MEMBER ATKINSON: Essentially it tells you how well it bioaccumulates or how well it goes into fatty tissues.

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ARB AIR POLLUTION SPECIALIST CHUNG: In this category points are awarded to substances that are the primary drivers of cancer or non-cancer health risk at facilities for which health risk assessment was required under the Air Toxics Hot Spots Program.

This category is not new, but we have reduced the maximum points possible because the risk assessment information is dated.

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ARB AIR POLLUTION SPECIALIST CHUNG: In this category, the basis for awarding points is the total statewide candidate toxic air contaminant emissions from mobile, industrial, and area sources.

PANEL MEMBER BLANC: Can I ask a question about

that?

How hard would it be to convert your tons per year into an equivalent molar exposure? I mean do we really care about the weight or do we care about how many molecules are out there?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Dr. Blanc, what we're trying to do is account for whatever information we have on exposure.

PANEL MEMBER BLANC: No, but wouldn't it be rather easy to weight that rather than by -- in other words you're giving importance to two factors - how much is released but how heavy the material is. And is that really what you want to do? Or do you care if there are a whole lot more molecules of a toxin out there? In other words would I care how many tons of tetrototoxin was released into the atmosphere or botulism toxin? No, I would care about how many molecules of botulism toxin.

Do you see what I'm saying? I mean you're obviously going to be --

PANEL MEMBER BYUS: Poor analogy, Paul. But I do agree with you.

PANEL MEMBER ATKINSON: I suspect the reporting data though is in tons or in --

PANEL MEMBER BLANC: No, I know. But you could convert it. I mean you just divide it by the molecular

weight or something.

I just throw it out for your consideration. Because you are going to then weigh towards things like zinc and other things that are inherently heavy but you may not care about.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: I see.

Dr. Blanc, that's actually a good --

CHAIRPERSON FROINES: Then that gets you into the problem of the -- I mean there are all sorts of problems with credit trading in air pollution -- and that's a good point -- of which it's one of a number that need attention if we're going to -- because the new Chair is very interested in trading credits. So is the Governor. And there are some real weak spots with that. And we should be conscious of that as we move forward.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Okay. The only thing that we would point out is that the California emissions are based on what we know about sources. That's actually how we derive the data, is through our database. So it's more tied towards sources. But I understand what you're saying. It's a good point.

Thank you.

Dr. Landolph.

PANEL MEMBER LANDOLPH: Of course there's all

kinds of ways to do this.

I'm wondering if you ought to add all the other things up and then multiply them by the emissions rather than just add the emissions, you know, to spread the numbers out. It's more like a tox -- it's something to think about.

Ideally what I guess you'd like is some toxicity slope factor for cancer times emissions to give you a hazard quotient. You might think about that a little bit, the multiplying rather than adding the emissions.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

Dr. Landolph, I think that's a good approach for chemicals where we have more information on toxicity and tea and health effects. But as we apply this to candidate chemicals, often times we don't have that information.

CHAIRPERSON FROINES: There's also another issue. And, that is, I've been working on the toxicology of diacetyl, which causes the bronchiolitis obliterans. And the flavorings industry released a report that said in flavorings there are 1200 chemicals used. Many, many, many, many, many aldehydes. And so we're right on target here. And so if you have a flavoring plan that's emitting 35 to 100 to 200 flavorings, then there should be some way to take that into consideration too. Because it may be that the toxicity from the release of all of that -- a

large number of compounds may be something of concern. And I don't have -- I'm not -- I don't have an idea of how you deal with it. But I know if you've got flavoring industries with very large numbers of chemicals, we ought to think about that.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Okay. Dr. Froines, That's a good suggestion.

I think what immediately comes to mind is we do have the "comment" column where we can account for at least some of that supplemental information that's not accounted for in the prior deciding spreadsheet.

ARB AIR POLLUTION SPECIALIST CHUNG: The photochemistry is one of the new categories in the proposed methodology. It's a 2-point category to account for what is known about the ability of a substance to react in the atmosphere to form other toxic air pollutants. If there's a reasonable amount of data to show that it can form other toxic air contaminants -- other toxic air pollutants in the atmosphere, it would receive 2 points. If there is suggestive evidence, we would give it 1 point.

Quantitative structure activity relationship models will be used where data are not available to determine if the products of photochemical reactions are expected to be of concern for toxicity.

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ARB AIR POLLUTION SPECIALIST CHUNG: Over the years, we found that the differences in data quality and availability between substance formerly identified as toxic air contaminants versus the major portion of the compounds on the Canada toxic air contaminants list was significant. We think we need to have some flexibility to allow for the consideration of data that does not fit neatly into the construct of the eight categories in the proposed methodology.

Our solution was to create a comment column, which lays out some broadly defined criteria for us to use as a basis for considering information that falls outside of the box.

This slide shows a few examples.

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ARB AIR POLLUTION SPECIALIST CHUNG: For exposure. Four factors not covered by the methodology are shown. Substance that displays all four factors would be awarded 4 points and so forth for substance displaying fewer factors.

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ARB AIR POLLUTION SPECIALIST CHUNG: For health effects, three factors not covered by methodology are shown. In this case substances that display irreversible

or severe adverse health effects would receive 4 points; 2 points would be awarded to substances that either amplify or potentiate an adverse health effect or has a moderate adverse health effect not captured elsewhere.

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PANEL MEMBER BLANC: So I think that where you need to think this through a little bit more, just looking at the examples you supplied to us for our edification, it just seems to be something that's breaking down in your comment health column. And I don't know if it's because I don't understand exactly how it's supposed to interplay with, let's say, the non-cancer toxicity score. The non-cancer toxicity score column has a very limited range of response and so many, many things are capable of getting a 4 on that. And I'm not sure what it is that's going to drive you to then award something, points in the health comments score column, but it seems to me that you're being very, very sparse or stingy with your attribution of points in that column, just looking at it quickly, trying to think through the chemicals.

I mean let's take something like silica, which I think you give 1 point in the comment score. Is that right?

CHAIRPERSON FROINES: In the what?

PANEL MEMBER BLANC: In the health comment box,

it gets 1 point, is that right?

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

I believe the current scoring is 1 point.

PANEL MEMBER BLANC: Okay. Here's a material which if you have a body burden of silica, you're more at risk of tuberculosis. That would seem to be something that would be something that potentiates other health effects.

In and of itself it causes a fatal lung condition of silicosis. It also causes another fatal lung condition called pulmonary alveolar prognosis. It is associated with more than double the risk of systemic rheumatologic disease. There's arguments about renal problems. I mean it's a little bit hard for me to see why is it that silica as just an example only got a point and then it's hard for me to see systematically how were you going to go through and somehow grossly determine the points that you award without going through a little mini-health hazard evaluation. It's not that I disagree with it conceptually. But I'm trying to figure out how you're going to do it in practice that's not going to be terribly subjective. In just judging on what you've done so far, it seems like there's some problems with it inherently.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA:

Yeah. Dr. Blanc, first of all I should point out

that what we've given you is work in progress. We actually haven't completed the entire scoring for the comment column yet. This is work that we're actually working with OEHHA to help us develop some of that information.

But would that be the kind of information that Dr. Blanc is pointing out, Bruce, would that be appropriate for the health column?

DR. WINDER: Yes, an example was -- for example, the lead, we're talking about severity. Same way with the issue you bring up in terms of the silicosa.

Again, we're talking about the document. And as I guess Jim was pointing out, this idea of a spread here for this point assignment was something that came up in our conversations with the leads. And we're just now applying this again to this list that you have before you. So that, as you said, is still a work in progress.

But I appreciate what you're trying to say: In some of these cases how do we capture without being terribly subjective, you know, the kinds of things you're mentioning? That's something we still have to think about. I'm not sure quite how to articulate all the criteria that would go into, say, the severity for the silica is 4 versus, say, 2, and that kind of thing.

PANEL MEMBER BLANC: Well, I mean I think the

severity -- in the severity, the non-cancer severity column where it's either a 0, 2, or 4, is that what it is again? Or could you be 1, 2, 3, 4 in the -- what?

ARB AIR POLLUTION SPECIALIST TAKEMOTO: Zero, 2, and 4, right. So 4 is if it can kill you and 2 is if it makes you sick and 0 is if it does nothing at all?

I mean does it have to be generally recognized as safe essentially to be a 0?

DR. WINDER: The idea there is it catches a 0 if its toxicity hasn't been captured elsewhere in the spreadsheet. So we're glad to hear that the comments are that -- this allows us to elaborate on these cases whether it's more severe for one reason or another or there's more concern than it's been captured in terms of just numbers of organ systems affected or whether it's children-specific or anything.

CHAIRPERSON FROINES: What slide is that?

PANEL MEMBER ATKINSON: It's a table in the --

CHAIRPERSON FROINES: Oh. Well, I think that having something -- and this is an oversimplification too. But if you had acute reversible and you had chronic reversible and if you had and if you had molecular biological and you had chronic irreversible, you'd have four nice categories. Because you could put liver toxicity, liver cirrhosis in chronic irreversible; you

could put atherosclerosis in chronic in irreversible; you could put cancer in molecular biological, and so on and so forth.

In other words, I think that -- I think that one can broaden those categories. And those four would be a good starting point.

Are you scowling?

PANEL MEMBER BLANC: No, I'm just -- I'm just thinking that you're -- you know, it's always a problem with these -- obviously with these weighting things because are you -- but you've recognized a problem, which is that your non-cancer toxicity scoring thing has very little spread in it and very little repertoire for capturing some things that matter more than others. So you've made this other column, which is okay, yeah, we know both these things can kill you, but based on human experience there's a whole lot more health problems with this other thing and so we're going to give it extra points, we're going to goose it up a little bit. And it may be that you need to do that and go farther or it may be that what John is suggesting is in the non-cancer toxicity scoring, that you could find a way of being more systematic in your initial toxicity that would -- that would be helpful. Or it may be, for example, chemicals for which it's clearly toxic in animal data but for which

there's virtually no human case reports of illness. And then there are other chemicals for which there's a myriad of human experience, unfortunately, that you would like to represent somehow in your weighting.

So I don't have a quick fix for it. But I can tell you that if you -- well, if you're going to rely on these last two columns and particularly on the comment health score, you better think through what's going to -- how you're going to award those and ask yourselves then will there be enough of a spread?

That's a 0, 1, 2, 3 -- that's a 0, 1, 2, 3, 4, so at least --

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Okay. That's a good comment, Dr. Blanc. We'll give that some --

CHAIRPERSON FROINES: Well, we'll work on this over the next two months.

I should tell you that when we did our study in the Caldecot Tunnel, we were able to differentiate the toxicity of the gasoline vapor from diesel vapor -- diesel -- pardon me -- cars versus diesel, and we found that gasoline particles were more toxic than diesel particles. And that you still get 90 percent of your diesel of course -- I mean the emissions from diesel are much greater than gasoline, but the relative toxic potency

shows that we found that the gasoline was more toxic. And Harvard's investigators have found the same thing. So that we have to -- when you -- you're going to have to add particles to your gasoline vapors, I think, so that we're looking at the whole picture, even though the amount of particles that come out of cars is very low, as we all know. Still, we'll show you our data -- we would testify with our data on any hearing.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Dr. Froines, just to point out that right now we currently have gasoline vapors on our candidate list, but it's gaseous components. We are considering adding gasoline exhaust, which we would take your comment in consideration and add that.

CHAIRPERSON FROINES: Then we'll have the same fight that we do with...

These proposed rankings are certainly a lot better than 1993. But, as Paul points out, there's still room for -- and we'll just work on it over the next couple of months, and I think we can come up with something.

PANEL MEMBER BLANC: I mean maybe the -- you know, this sort of fits into with our speaker from the FDA. But if you take the 23 ones that have already been identified and use them as your testing ground and make sure that your system assigns them higher ranks than they

actually seem to have currently, that would be one way of refining the system, particularly, by the way, in terms of these comments health score and comments exposure score. That would be one area in particular. I am amazed that so few of those have any points at all in the health column score. And, in fact, the most of any of them had is a 1. And that's only for a couple of them. I mean what does vinyl chloride have to do not to get comments from you in the health score, for example?

PANEL MEMBER FRIEDMAN: One fairly reassuring thing is that environmental tobacco smoke and diesel appear now in the high rankings, and they didn't before.

I assume these are the top -- are these the top 10 or --

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: Yes, they are, Mr. Friedman.

PANEL MEMBER FRIEDMAN: Yeah.

ARB SUBSTANCE EVALUATION SECTION MANAGER AGUILA: And, you know, they will somewhat change a little once we complete our scoring, because it's kind of unfair that we've given you work that's still in progress.

CHAIRPERSON FROINES: Well, I think that what -- I feel that -- I know you folks have been very busy with a wide ranging number of activities. But I think if we worked over the next two months, I think we can get

something that we can sort of say it's been a long time but we're sort of there. And we may have to change it later. But let's bring it to closure this time, and I think we'll all feel good about that.

And then you have to get your management to start sending things forward to us. And we'll hold our breath.

PANEL MEMBER BLANC: Be careful what you ask for.

(Laughter.)

CHAIRPERSON FROINES: Well, thank you very much. It's very useful. I think the Panel will look this over and find it very interesting and think about the things that have been raised.

PANEL MEMBER BLANC: So would you like to consider a motion for adjourning?

CHAIRPERSON FROINES: Well, we would consider a motion to adjourn.

PANEL MEMBER BLANC: So moved.

CHAIRPERSON FROINES: So moved. You didn't make that motion last night.

Any seconds?

PANEL MEMBER ATKINSON: I'll second it.

CHAIRPERSON FROINES: All in favor?

(Ayes.)

CHAIRPERSON FROINES: Unanimous.

The meeting is adjourned officially.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 3:20 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 17th day of December, 2007.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063